DANISH MEDICAL BULLETIN

A SURVEY OF DANISH MEDICINE

PUBLISHED BY

UGESKRIFT FOR LÆGER

THE MEDICAL FACULTIES OF THE UNIVERSITIES OF COPENHAGEN AND AARHUS

THE NATIONAL HEALTH SERVICE OF DENMARK

CONTENTS

Subscription: Ejnar Munksgaard, 6, Nørregade, Copenhagen, Denmark

Price: In Scandinavia Dan. Crowns 15.00, in Europe £ 1/-/-, Outside Europe $ 3.00 or Equivalent

Free of Charge for Medical Institutions on Request

VOL 1
JUNE 1954

A Publication of
THE DANISH MEDICAL ASSOCIATION
Domus Medica, Copenhagen Ø, Denmark

NO 3
PAGES 61-92

VOL 1 NO 3 **DANISH MEDICAL BULLETIN** JUNE 1954

ON THE FREQUENCY OF DIABETES MELLITUS IN DENMARK

By MARIE LINDHARDT

Diabetes mellitus is a disease which has attracted increasing attention in Denmark and several other countries during the past twenty years or so. Not only is the medical profession itself going more and more in for specialization in the study of the disease, but matters have taken a more social turn: diabetics are forming nation-wide associations for the dual purpose of disseminating information as to treatment and of making their position stronger in their various demands upon the public health authorities. Collections are organized for establishing institutions for the treatment and nursing of both children and adults — "sugar diabetes" to some extent has become a "national" disease like tuberculosis, cancer, rheumatism and others.

The cause of this greater interest in diabetes mellitus is naturally its increasing frequency. As always when a disease changes in its behaviour, it is difficult to decide how much weight ought to be attached to improved diagnostics; but as diabetes mellitus is a disease which can now, and at any rate during the past twenty odd years could, be diagnosed with a fairly high proportion of certainty, it would seem to be a fact that there has been a real increase in the number of cases, an increase greater than the growth of the population. The disease has its highest frequency among elderly people, and therefore, the increasing length of life must be contributing greatly to the greater incidence. Moreover, the life-prolonging effect of insulin must have increased the number of diabetics living in our generation.

There are no definite figures of the number of diabetics in Denmark. Nevertheless, as will be seen from the following, physicians and statisticians have made estimates and representative censuses leading along different routes to pretty much the same results, i. e. that about 4 per thousand of the population of Denmark (1953 4.3 millions) are diabetics.

Regarding the mortality of diabetes mellitus, the official death-cause statistics of the various countries generally provide comprehensive information as to the number of deaths according to sex and age, etc. In many places, however (including Denmark), the figures are of deaths *among* diabetics and not deaths *from* diabetes (coma diabeticum). In the following a reference will be made to the methods which have been employed in order to clarify this question and the results achieved.

NUMBER OF DIABETICS IN DENMARK

The one direct census of diabetics in Denmark as a whole was made by the National Health Service in 1927, when questionnaires were sent out to every physician in the country. The primary purpose of that investigation was to establish figures to show the insulin required. The number returned, 4,247 or 12 per 10,000 of the population, was presumably a minimum number, as is usual in returns of this kind. The statistical analysis of the material, made by Robert Nielsen, revealed an increase towards the higher age groups and a small preponderance of females, the sex ratio being 49.4 males to 50.6 females.

In 1949 and 1950 Horstmann and Christensen respectively made a count of diabetics in a Funen and a Jutland county through the medium of questionnaires to physicians, and on that basis they both arrived at a calculated number of 16,000 for the whole country, or 38 per 10,000. Both authors found more diabetics in the towns than in the rural areas. In Horst-

From the Danish National Health Service.

mann's material the sex ratio was 43.3 males and 56.7 females, in Christensen's it was 38.8 to 61.2.

Quite recently statistical material of an entirely different character was examined for the purpose of arriving at a satisfactory figure for the diabetic population. The National Health Service together with the National Diabetes Society, represented by Dreyer and Hey, went very thoroughly through a file of diabetics who had been issued with ration cards for synthetic sugars in the period from February 1, 1944 to October 20, 1948. With the aid of the public registers the material was carefully revised and July 1, 1946 was chosen as the critical date. After the removal of cards for people who had died prior to that date, the original 22,500 cards had been reduced to 17,223, which then were assumed to represent the diabetic population in Denmark in 1946, a figure corresponding to 43 per 10,000 (see Table 1).

Table 1.

Occurrence of diabetes mellitus in Denmark July 1, 1946 (Dreyer and Hey).

	Actual numbers			Frequency per 10,000 pop		
	Towns	rural areas	entire country	Towns	rural areas	entire count
Males	4523	3144	7667	49	29	38
Females	5625	3931	9556	55	39	47
Total	10148	7075	17223	52	34	43

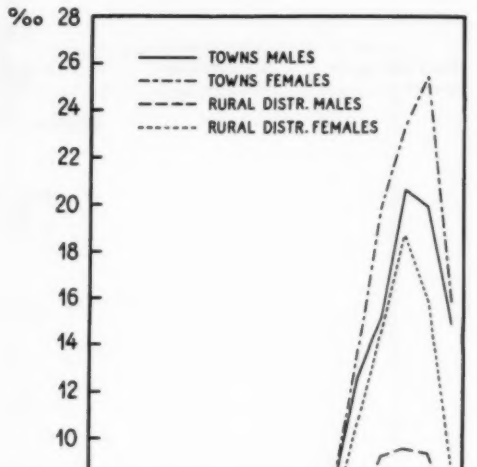


Fig. 1.

Frequency of diabetes mellitus in Denmark July 1, 1946 per 1,000 population according to sex and age in towns and rural districts. (Dreyer and Hey).

The sex ratio was 44.5 males to 55.5 females, figures which differ somewhat from some of the investigations already mentioned but which nevertheless confirm the great preponderance of females. As will appear from fig. 1, diabetes mellitus is distinctly associated with high age. The female preponderance does not appear until after the menopause and the peak is reached at the age of 60—70, a peak that is most marked in the towns. The difference in frequency in town and country, also observed by previous authors, is so pronounced that diabetes morbidity among males in the towns is everywhere higher than among females in the rural areas, even among the very old. At the age of 55 and over there are relatively twice as many male diabetics in the towns as in the rural areas. The difference between males and females is 0.9 per thousand, whereas the difference between town and country is 1.8 per thousand — both of which are significant differences.

The terms urban and rural areas in Denmark are rather historical in their determination. The position is that many towns are so small that their population is considerably less than those of urban areas or town suburbs representing complete, built-up areas. Administratively the latter still belong to the rural areas because their growth dates from the past half century. Nevertheless, a comparison of the figures for Denmark's only large city, Copenhagen-Frederiksberg (aggregating 877,500 inhabitants in 1953) with those of the other urban communities shows that there is no great difference in the occurrence of diabetics. From this it may perhaps be permissible to conclude that it is the living conditions in the rural areas, which form the great majority of the rural communes now under discussion, that make the population less susceptible to diabetes.

This attempt at estimating the number of diabetics in Denmark is somewhat inexact because the estimate of the number of child diabetics is undoubtedly too low. In the first place, Horstmann and Christensen in their materials, collected with the aid of the local physicians, have relatively more children for the two counties, and in the second place the number of diabetic school children, now accounted for several parts of the country, shows that the number of children in the diabetic population has to be increased. On the basis of this information Dreyer and Hey put the discrepancy in the registration of children at between 300 and 400. Roughly speaking, the country's diabetic population in 1946 may be evaluated at about 18,000, or 44 per 10,000 of the entire population.

The *Morbidity Survey* made of the Danish population in the period from 1951 to 1954 has now also provided an account of the frequency of diabetes mellitus for the first year. This survey (details of which will not be discussed in the present context), shows that among adults — persons of over 15 years of age — the frequency is 50 per 10,000 of the population. In Dreyer and Hey's material the figure for adults was 56 per 10,000 people of over 15 years. The sex ratio was 40.3 males to 59.7 females. The agreement between the two results is not bad, considering that from the morbidity survey the figures are as yet small for the first year of investigation. For the rest, a look at these numbers leaves the impression that the morbidity preponderance among females increases with time. In the first return of 1927 there were almost equal numbers of males and females, whereas at the last survey there were 50 per cent more females than males.

MORTALITY OF DIABETES MELLITUS

Since the disease is a chronic one, remaining with its victims till their death, it is of interest to know whether the lifespan of these patients as diabetics differs from that of the general population, and to what extent it is the disease itself, diabetes mellitus, that is the actual cause of death.

On this we have two thorough analyses, one by Franz Heintzelmann, the other by Dreyer and Hey, the latter's in continuation of their earlier work already referred to. As a background for these studies it will be helpful to give the figures from the official Danish statistics of causes of death (see Table 2), to which have been added for comparison the figures arrived at by Heintzelmann, which will be explained below.

Table 2.

Diabetes mellitus mortality in Denmark, 1921—53.

	Actual numbers		Deaths per 100,000 population	
	Official statistics	*Heintzelmann*	Official statistics	*Heintzelmann*
1921-30 ann. aver.	467	—	13.6	—
1931-40 » »	723	—	19.5	—
1941-46 » »	714	—	18.0	—
1947	789	900	19.0	21.7
1948	695	769	16.6	18.3
1949	856	951	20.2	22.5
1950	966	—	22.6	—
1951	294	—	6.8	—
1952	229	—	5.3	—
1953	222	—	5.0	—

The figures of the official statistics are greatly affected by changing methods of registration and also by the phrasing of the questions on the death certificate itself regarding the cause of death. In the decade 1921—30 a special Danish nomenbeen in use since 1876. The entire period had a fixed number for diabetes mellitus. On the death certificates forming the basis of the statistics there was the simple question as to the cause of death and its complications. In 1931 there were introduced both a new death certificate form and a new inter-Scandinavian nomenclature, one that was very similar to the internationale one. On the death certificate used from 1931 to 50, a distinction was made between principal disease with complications and immediate cause of death, and certain fixed rules were observed in coding the diseases. These were to the effect that when the diagnosis diabetes mellitus was shown on the death certificate, it would be registered as the cause of death unless violent death, cancer, tuberculosis or certain infectious diseases were diagnosed simultaneously.

The international death cause nomenclature has been in use since 1941, but the procedure of coding the diseases was the same as before.

In 1951 the death certificates were again amended and a certificate formulated according to international rules was introduced to Denmark as to many other civilized countries. The new formulation aims at finding the basic cause of death and all complications as well as all conditions likely to have been contributory to the death.

Simultaneously with the introduction of this much improved death certificate the new international disease classification of 1948 was adopted, and by following its rules for coding the causes of death we are now much better able to establish which deaths among diabetics are directly due to diabetes.

The change in 1931 brought about a considerable increase in the mortality figures, one that continued until 1936. Since that year the figures have been very steady at about 20 per 100,000 population — until they fell abruptly from 966 deaths in 1950 to 294 in 1951, corresponding to 22.6 and 6.8 per 100,000 population. In 1952 and 1953 the number was still lower.

From these figures taken from the official statistics it would seem difficult to arrive at a reliable statement of the mortality of diabetes mellitus. Heintzelmann therefore undertook an examination of a number of death certificates, in all 2,620 for the years 1947—49, having for these three years picked out all deaths on whose certificates any mention at all was made of the diagnosis diabetes mellitus. This gave him a larger number of deaths than the official statistics (see Table 2), there being a number of diseases which, according to the system of coding then followed, had a preferential right over diabetes mellitus.

Table 3 shows Heintzelmann's calculated death rates according to sex and age. The total sex ratio is 38.7 per cent for males to 61.3 per

cent for females. The marked difference in the mortality in the various age groups and for the two sexes shows how greatly the magnitude of a sex ratio depends upon the age composition of the material.

Table 3 *(Heintzelmann).*

Mortality of diabetic patients according to age and sex. 1947—1949.

Rates per 100,000 population.

Age	males	females	total
under 10 years	0.6	0.8	0.7
10—14 years	0.4	0.9	0.7
15—19 »	0.2	2.7	1.5
20—24 »	0.9	2.4	1.7
25—34 »	2.3	3.0	2.7
35—44 »	5.0	2.4	3.7
45—54 »	10.4	10.5	10.4
55—64 »	39.0	57.3	48.3
65—74 »	109.2	180.9	146.5
75—85 »	164.9	226.1	197.9
85 years and over	84.5	162.2	129.2
Total..	16.1	25.5	20.9

When referring to the size of the diabetic population it was shown that there were more diabetics among females than among males and that the distribution was greater in the urban than in the rural areas. The same applies to the mortality.

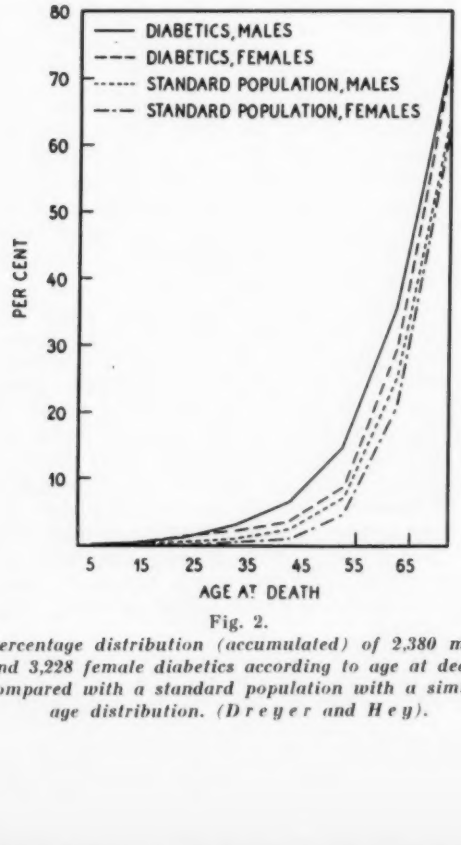


Fig. 2.

Percentage distribution (accumulated) of 2,380 male and 3,228 female diabetics according to age at death, compared with a standard population with a similar age distribution. (Dreyer and Hey).

Dreyer and Hey have analyzed the mortality details for diabetics in another manner. From the material mentioned they have found that in the period from February 1, 1944 to July 1, 1951 there were 6,065 deaths, of which the age at death was known for 5,608, made up of 2,380 males and 3,228 females. In fig. 2 the relative distribution of these deaths according to age at death is shown clearly in curves, of which the ordinate indicates the percentage of deaths within a given age. For comparison, curves have been plotted showing conditions in the population as a whole. From this it appears that diabetic males die earlier than diabetic females, as is the case in the total population, and that diabetics die earlier than the general population.

Unfortunately the available material will not permit of compiling a real life table of diabetics, nor have we the age of the patients at the onset of the disease or its recognition. It is the intention of Dreyer and Hey further to utilize the copious numerical material by following the individual diabetics through a series of years in order to clarify these aspects of the diabetes statistics.

It will be apparent from the foregoing that in only the fewest cases is coma diabeticum the actual cause of death of a diabetic. In his material of 2,620 death certificates Heintzelmann has made a recoding of the causes, according to which the number of deaths from diabetes mellitus was 207, or only 7.9 per cent of the entire group. Dreyer and Hey, by re-registering the death causes for 1,539 persons in their material for whom the death causes were known, found a quite similar proportion, 6.8 (see Table 4). In the statement of the other causes of death there is close conformity between the two calculations, with a single exception. Cancer was this exception. While Heintzelmann found this death cause in 4.8 per cent., Dreyer and Hey found it in 9.7 per cent.

Table 4.

Percentage distribution of causes of death among diabetics and in total population of Denmark.

Cause of death.	2,620 diabetics 1947-49 *(Heintzelmann)*	1,539 diabetics 1944-51 *(Dreyer & Hey)*	Standard population with same age distribution as diabetics in Dreyer & Hey's material
Diabetes mellitus ..	7.9	6.8	0.6
Renal diseases.....	11.2	9.7	2.0
Cancer	4.8	9.7	19.9
Cardiac diseases	34.7	36.1	17.2
Respiratory diseases	6.9	5.4	3.2
Arteriosclerosis	20.6	18.8	28.7
Tuberculosis	3.4	1.6	1.2
Other causes	10.5	11.9	27.2
Total..	100.0	100.0	100.0

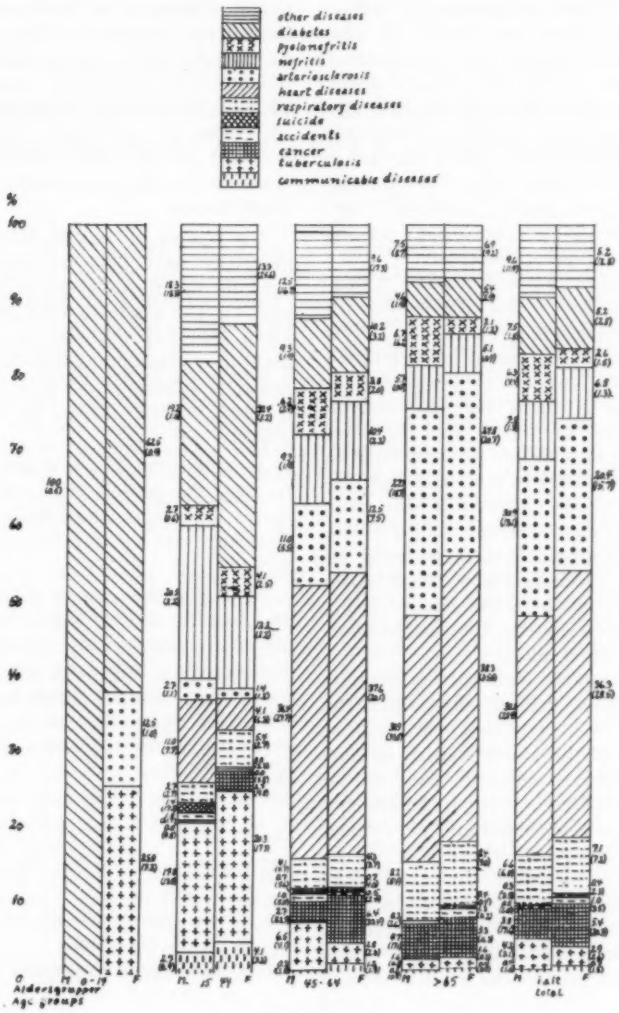


Fig. 3.

Percentage distribution of deaths among 2,620 diabetics according to age, sex and cause of death. 1947—49. (Heintzelmann).

This disagreement was presumably due to the different geneses of the two materials. The death certificates analyzed by Heintzelmann were selected according to whether the diagnosis diabetes mellitus appeared at all upon them, whereas Dreyer and Hey's basic material is deaths among persons known to have suffered from diabetes mellitus, regardless of whether or not this was mentioned on the death certificate. Heintzelmann ascribes the low cancer mortality in his material inter alia to the circumstance that an aggravation of a diabetic's condition may possibly be laid at the door of diabetes mellitus, so that the doctor will not diagnose the cancer at all. As Dreyer and Hey point out, however, it is conversely probable that in a cancer death it will be the diabetes that is not mentioned on the death certificate. Where renal and cardiac disease is the primary cause of death, the two authors consider there is greater probability that diabetes mellitus will also be mentioned.

Dreyer & Hey's assumption is verified by Joslin, who for the period 1937—43 shows 8.8 per cent deaths from cancer in a study of 2,583 deaths among diabetics in his own clinic.

The diseases or disease groups in Table 4 occur with very different weights at the various ages. For example, deaths of children are preponderantly due to the disease coma diabeticum itself. Thus when the official Danish death cause statistics show that the mortality of diabetes mellitus in the age group 0—14 years has fallen very heavily,

from 2.8 deaths per 100,000 population in 1921—30 to 0.5 in 1946—50, there can hardly be any doubt that this decrease, which must be credited to insulin, is quite real and that the cause of death there is diabetes itself. In the age groups immediately following, diabetes mellitus occurs still as the most frequent cause of death, but on a declining scale, and diseases like tuberculosis and renal affections now begin to assert themselves. Among the oldest the dominating causes are cardiac disease and arteriosclerosis.

In fig. 3 Heintzelmann gives the details of the relative distribution of the causes of death according to sex and age.

In Table 4 a comparison is made between death causes among diabetics and the total population, and, considering the unequal age distribution in the two populations, Dreyer and Hey for the latter group have calculated the mortality in a standard population with the same age distribution as the diabetic group. As might have been expected, the mortality of diabetes mellitus here is much lower than among diabetics, whereas the degenerative diseases, cardiac and renal affections, are much higher than in the general population — again as anticipated. The discrepancy as to cancer is mentioned above.

There are many accounts from other countries concerning the mortality of diabetes mellitus, but the materials employed there are nearly all so different from those of the above Danish authors that direct comparison is generally out of the question. In most cases they are selected materials concerning hospital patients, post mortem returns etc. The nearest to the Danish surveys is one by the Norwegian Hanssen, who has worked with a total of 392 deaths among diabetics in the town of Bergen in the years 1925—41. This relatively small but homogeneous material, from a single town, in its general outlines has results similar to those found by Heintzelmann, quoted above.

SUMMARY

Prompted by the increasing spread of diabetes mellitus in Denmark various authors have endeavoured in different ways to calculate the number of diabetics and deaths among them.

The different investigators have arrived at about the same result, i. e. that there are about 18,000 diabetics in Denmark, corresponding to about 4 per thousand of the population. There are more diabetics among females than among males, and the frequency rises with age in both sexes. The preponderance of females does not appear until after the menopause. Diabetes mellitus is less common in the rural areas proper than in the towns, regardless of whether they are large or small towns.

The figures of the official statistics for diabetes mortality have been affected through the years both by the formulation of the death certificates and by the classification of death causes used. Until 1951 the mortality was principally a statement of deaths among diabetics, after which a new death certificate and a new classification ensured a more correct return of mortality from coma diabeticum.

A calculation of the general mortality of diabetics for the period 1944—51 shows that diabetic males die earlier than diabetic females, and that diabetics die earlier than the population as a whole.

Regarding the causes of death among diabetics, the Danish studies show that 7—8 per cent of all deaths are due to coma diabeticum. A comparison with a standard population gives a mortality from diabetes about ten times higher among diabetics than among the general population, whereas cardiac and renal diseases are at a much higher level.

References:

1) *Christensen, Jørgen:* Ugeskrift for Læger 1953, *115:* 528.
2) *Dreyer, Karen* and *Alfred Hey:* Ugeskrift for Læger 1953, *115:* 1069.
3) *Dreyer, Karen* and *Alfred Hey:* Ugeskrift for Læger 1954, *116:* 273.
4) *Hanssen, P.:* Diabetes Mellitus in Bergen 1925—1941. Thesis, J. Grundt Tanum, Oslo 1946.
5) *Heintzelmann, Franz:* Ugeskrift for Læger 1952, *114:* 555.
6) *Horstmann, Paul:* Ugeskrift for Læger 1950, *112:* 1437.
7) *Joslin, Elliott:* Treatment of Diabetes Mellitus. London 1946, p. 653.
8) *Nielsen, Robert:* Ugeskrift for Læger 1928, *90:* 850.

THE INCIDENCE OF VASCULAR DISORDERS IN DIABETICS SURVIVING 15—25 YEARS AFTER ONSET OF THE DISEASE

By KNUD LUNDBÆK

With the introduction of insulin into therapy the mortality of diabetics fell abruptly. The severe diabetic, who would hitherto have succumbed to the disease in a matter of a few months, now survived for many years.

Ten years after the discovery of insulin it became apparent that the clinical picture of the diabetic population was undergoing a change: the vascular »complications« seemed to be increasing in frequency. In 1935 W a i t e and B e e t h a m demonstrated the close relationship between the duration of the disease and the incidence of diabetic retinopathy (1).

During the forties a number of reports were published, dealing with the incidence of the various vascular disorders in diabetes of long standing. Usually the information contained in these publications was based upon the study of highly selected series of patients, visiting one hospital or one hospital department. When in some series of this character extremely high incidences of the very severe forms of vascular disease were obtained, it is probable that this was true because the very ill patients came to the hospital *on account of* their grave disabilities.

In an endeavour to furnish a true and representative picture of long-term diabetic vascular disorders we have collected a series of cases consisting of unselected diabetics, living in Aarhus, who had been suffering from diabetes for 15—25 years.

A Danish patient who has had diabetes for more than 15 years will usually have been admitted to a local hospital once or several times in the course of the years. Most diabetics are sent to the hospital for the initial adjustment of treatment or general training as soon as the diagnosis is made. Many will of course have been admitted later on in coma, insulin shock, with vascular disorders or intercurrent diseases.

At first, therefore, all the case records from the various hospital departments admitting Aarhusian patients were scrutinized, and all cases of diabetes dating from between 1924 and 1935 were collected. Two checks were made on the completeness of the series: a letter with a list of the cases found in the records was sent to all practitioners in Aarhus and neighbouring communities, asking for possible omissions, and at a meeting of the local section of the National Association of Diabetics, attended by some 400 diabetics, patients not on our list were asked to give notice.

By these procedures we obtained a total of 234 cases. From the Public Registration Office we received the addresses of the 165 patients who were still alive. The remaining 69 patients had died after having had the disease for at least 15 years. Useful information was secured on most of the dead, but in the present report we shall not deal with the findings in this group.

The 165 living patients were requested to appear for medical examination, and all of them came.

The examination comprised a meticulous history of the disease, checking of notes taken from the case records, a general physical examination, including ophthalmoscopy in mydriasis, and determinations of height, weight, blood pressure, capillary resistance, sedimentation rate, haemoglobin, serum protein, and serum cholesterol. The urine was tested for sugar, ketone bodies and protein, and examined microscopically. Only one patient was found to have a slight ketosis at the time of the examination.

The result of this follow-up has been published in detail elsewhere (2). In the present report a short summary will be given of the incidence of the various vascular anomalies found among the patients who were alive at the time of the follow-up.

RESULTS

Figure 1 is largely self-explanatory. It is seen that about two thirds of the patients were found to have *simple retinopathy*, i. e. the nonproliferative form of diabetic retinopathy. The degree of morphological anomaly ranged from a few »sangvinolent spots« (microaneurysms) to severe cases with »dots and blots« and large exudates. No significant difference was found between the incidence in young, middle aged, and old patients.

The severe *proliferative form of diabetic retinopathy* was found in only 6 per cent of the patients, equally distributed in the three age groups.

Blindness due to diabetic eye disease was found in only 3 per cent of the patients.

Chronic nephropathy was defined as the occurrence of an abnormal number of red cells and/or casts in the urine — as the only finding, or combined with hypertension, proteinuria and oedema. This anomaly occurred in about one fourth of the patients. It looks as if chronic nephropathy was more prevalent among the oldest patients, but no

From the Second Medical University Clinic, Kommunehospitalet, Aarhus, Denmark.

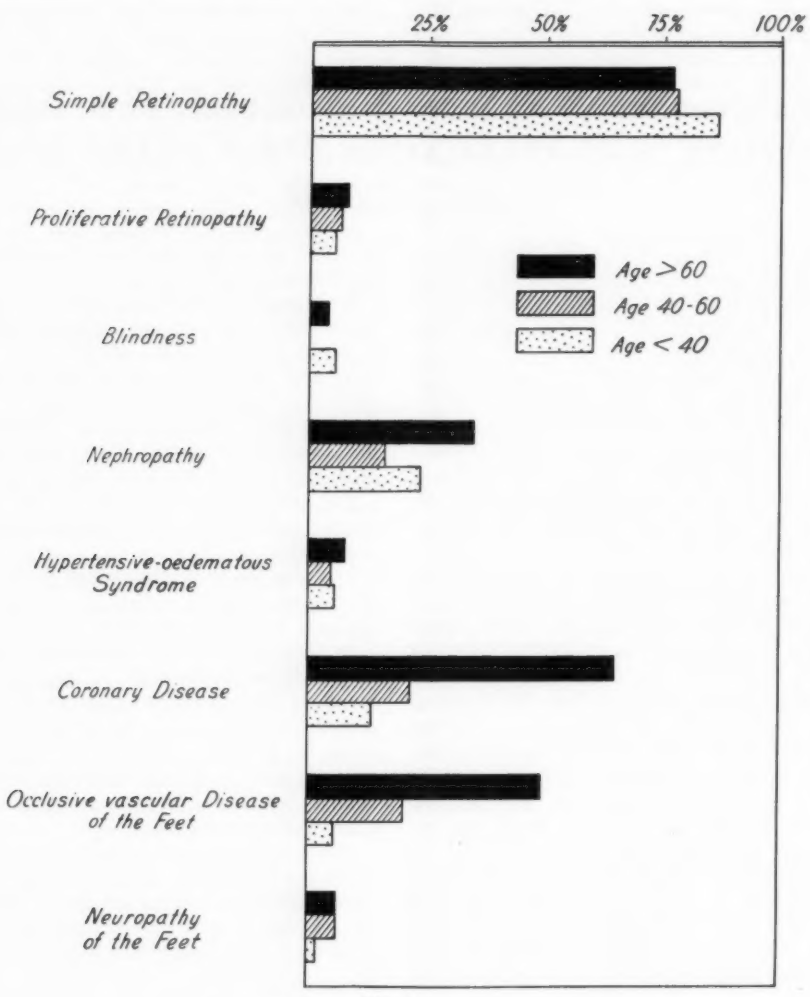


Fig. 1.
Percentage Incidence of Long-term Diabetic Disorders in an Unselected Series of Cases.

significant difference could be ascertained by statistical analysis of the figures. — Proteinuria occurred in more than 90 per cent of the cases of chronic nephropathy thus defined, and an abnormal number of leukocytes was found in 91 per cent of the men, 95 per cent of the women with nephropathy.

The hypertensive-oedematous syndrome, including heavy proteinuria (the Kimmelstiel-Wilson syndrome) was found in only 6 per cent of our series. All except one of these patients have died since the time of the follow-up.

Coronary disease (abnormal electrocardiogram, cardiac failure or typical angina pectoris) was found very commonly among the patients above 60 years of age (65 per cent). In the younger age groups it was much less frequent, and in patients less than 40 years old only 13 per cent had symptoms or signs of coronary disease. These young patients also always had very severe lesions of the eyes and the kidneys. The difference between the incidence in the oldest and the younger age groups is statistically significant. — Four fifths of the patients with coronary disease had marked symptoms.

Occlusive vascular disease of the feet also showed a much higher incidence among the old than among the young patients. In the oldest age group 49 per cent of the patients had peripheral vascular disease, in the youngest group only 5 per cent. Here also the statistical analysis reveals a highly significant difference.

Diabetic neuropathy has been defined in many different ways by different observers. By numerical analysis of such findings as tingling, burning pains, loss of tendon reflexes, loss of sensibility etc. it proved impossible to base a clear-cut nosological entity on anything else than

the objective finding of reduced tactile sensibility. This anomaly was found in only 5 per cent of the cases. The figures are too small to show any possible correlation between age and neuropathy. It was noticeable that subjective complaints suggesting neurological disturbances were equally frequent among patients with and without objective signs of nervous lesion. No case af generalized diabetic neuropathy with pareses, involvement of the bladder and intestines, etc. occurred in this series.

No sex difference was found in any of the disorders mentioned.

No significant correlation could be shown between the incidence of the disorders, and the age of the patient at the time of onset of the disease.

DISCUSSION

It appears that the various vascular anomalies in long-term diabetes are found with highly different incidences.

Retinopathy ranged much higher than any other disorders and in fact is found in most diabetics after 15—25 years of diabetic life. The reason for this probably is that the retina is the only organ (except the conjunctiva) where the vascular bed can be inspected directly and where consequently even minute changes can be observed. Proliferative retinopathy and blindness (often due to retinal proliferations) are not very common after 15—25 years' duration of the disease.

Signs of chronic kidney disease were common, but the severe oedematous forms are rare. We know, however, from autopsy studies that histological anomalies (the Kimmelstiel-Wilson lesion) are present about as often as retinopathy in such patients.

Coronary disease and occlusive vascular disease are found very often among the older patients, very seldom in the young ones.

Neuropathy, by our definition, is of rare occurrence.

Elsewhere (2, 3) reasons have been given for regarding the vascular lesions in long-term diabetes as various expressions of a specific diabetic anomaly, a diabetic angiopathy. This point of view of course does not imply that common diseases such as atherosclerosis or medial sclerosis are rare or absent in diabetics. As a matter of fact the above chart (fig. 1) clearly demonstrates the importance of pure diabetic versus mixed vascular disease, in long-term diabetics.

Retinopathy and nephropathy occur with equal incidence in young and old patients. The percentage of patients having coronary disease and occlusive vascular disease of the feet increases with age.

Now diabetic retinopathy is certainly neither atherosclerosis nor medial sclerosis, but a unique morphological pattern, occurring only in diabetics. The same is true about the histological changes of the kidneys in diabetic nephropathy. Even if we cannot argue from the histology in our series, it seems reasonable to assume that the lack of correlation between age and nephropathy means that this anomaly is largely a purely diabetic one.

On the other hand, the marked positive correlation between the incidence and age in the patients suffering from coronary and peripheral vascular disorders points to the fact that in these localizations we are dealing with mixed forms. In the coronary arteries it is probably a mixture of atherosclerosis and diabetic angiopathy. In the lower extremities a medial sclerotic element must also be assumed. We know that atherosclerosis is related to age, and medial sclerosis is probably a simple expression of age.

It might be thought that the best way of viewing these matters would be to accept the retinopathy and possibly the nephropathy as true diabetic disorders, while regarding the lesions of the heart and the feet as non-diabetic, age-related disorders.

There are several points, however, which disprove this simple idea. It is only necessary to mention two of them here: 1. the fact that the incidence of coronary and peripheral vascular disease in all age groups is much higher among diabetics than among non-diabetics. 2) the fact that the incidences of these disorders in our material are linked up statistically with the incidences of retinopathy and nephropathy.

The general picture, as it appears from this study, is perhaps less dark than some clinicians have feared. Especially the marked difference between the very large number of cases in which abnormal findings are present and the much smaller number of cases where these anomalies give rise to discomfort or even disability is rather striking.

It should be stressed, however, that a future study, after 5 or 10 more years, will probably reveal a graver situation. The fate of most of the patients in our series is known to us, and already by now the occurrence of disabilities has gone up considerably.

It is not the purpose of this brief paper to discuss the intricate problems of the nature of diabetic angiopathy or the importance of diabetic control for the prevention of it. It should however be mentioned that our studies have provided evidence which seems to suggest that proper treatment of the metabolic disturbances in diabetes mellitus has *some* effect on the development of long-term diabetic manifestations.

SUMMARY

A report is given of the incidence of various vascular disorders in a representative and unselected series of diabetics who have survived for 15—25 years after the onset of the disease.

It is important to note the difference between the very high incidence of some demonstrable

lesions, and the much lower incidence of incapacitating disease.

The findings point to the possibility of distinguishing between vascular areas with pure diabetic angiopathy and areas where mixed vascular disorders are found.

References:

1) *Waite, J. H. & W. P. Beetham:* New Engl. J. Med. 1935, *212:* 367, 429.
2) *Lundbæk, K.:* Long-term Diabetes (ophthalmological Section in Collaboration with V. A. Jensen). Copenhagen, London, New York, 1953.
3) *Lundbæk, K.:* Lancet 1954, *I:* 377.

THE PROTEIN-BOUND CARBOHYDRATES IN SERUM FROM DIABETIC PATIENTS AND THE RELATION TO THE DURATION OF DIABETES AND THE VASCULAR COMPLICATIONS

By GERTRUD HJELM NIELSEN and JACOB E. POULSEN

It has been found that in certain diseases the amounts of plasma protein-bound carbohydrates vary from the normal. Increased values have been reported in tuberculosis, cancer (Seibert, Pfaff, and Seibert (1948). Greenspan, Lehman, Graff, and Schoenbach 1951) and myocardial infarction (Simkin, Bergman, and Prinzmetal (1949). Israel, Webster, and Maher 1949).

Regarding protein-bound carbohydrates in blood from diabetics few observations have been reported. In 1949 Jacobs examined the bound glucosamine of serummucoid, and he observed fluctuations under the influence of insulin; the blood-plasma was coagulated by heat, and after centrifugation the protein in the supernatant fluid was hydrolised. He measured the colour produced by the method generally used for glucosamine estimation. The changes of glucosamine in deproteinized plasma followed the blood-sugar changes produced by insulin.

This method has later been found to be unreliable because the non-protein-bound carbohydrates and aminoacids of the plasma are not removed and influence the reaction (Immers and Vasseur 1952).

Stary, Kaleoglu, and Bursa (1951) measured the protein-bound polysaccharides by means of the orcin method. They report elevated values in untreated diabetics and a gradual normalization by fasting or by sufficient insulin treatment. They do not correlate the vascular lesions of kidneys and eyes to the values of plasma protein-bound polysaccharides.

Recently Berkman, Rifkin, and Ross (1953) published a paper on the serum polysaccharides in 66 diabetic patients with and without degenerative vascular disease. They measured the non-glucosamine polysaccharides with anthrone and furthermore they examined glucosamine and serum mucoprotein. In diabetics without vascular lesions they found concentrations within normal limits. In diabetics with degenerative vascular disease they found increased values of polysaccharides and glucosamine bound to serum proteins. In diabetics and non-diabetics with renal disease they found comparable variations of the carbohydrate to the protein ratio of the mucoproteins. No uniform relationship between blood-sugar levels and the various serum polysaccharide substances was found.

A similar study made by Keiding (1953) has shown higher concentration of the protein-bound carbohydrates of serum from diabetics with vascular complications as compared to a group of diabetics with no or minimal complications. Also the latter group showed elevation of the protein-bound carbohydrates when compared to a group of non-diabetics. In the same study a decrease in total protein concentration was found concomitant to the elevation of the protein-bound carbohydrates.

Instigated by the histological findings in organs from patients with long-standing diabetes in which complex carbohydrate substances have been demonstrated, an examination of the protein-bound carbohydrates in plasma was planned.

The aim was to evaluate a possible correlation of blood-serum protein-bound carbohydrates to the development of vascular lesion. The results are in accordance with Berkman, Rifkin, and Ross. We have found elevated values in patients with vascular lesions, and in uncomplicated diabetics insignificantly increased values without relation to the duration of diabetes. Furthermore some problems regarding the degree of complication, and the influence of treatment are discussed.

We have measured:

1. the protein amount of a) serum, b) precipitate after 50 per cent saturation with ammonium sulphate, and c) the filtrate after the pre-

From the Steno Memorial Hospital.

cipitation with 50 per cent saturation with ammonium sulphate;

2. non-glucosamine carbohydrate obtained after hydrolysis with sulphuric acid of the three serum protein samples;
3. the glucosamine amount of the three serum protein samples.

MATERIAL

All patients included in this material were hospitalized. General physical examination was performed and all the patients were submitted to various routine investigations including ophthalmoscopy, X-ray of the chest, measurement of the blood pressure, the sedimentation rate, hemoglobin, and tuberculine test, eventually X-ray of the legs and electrocardiography. If one or more of the symptoms of hypertension, proteinuria and edema were present, the blood-urea was estimated. All the diabetics were followed with blood-sugar estimations, 5 to 7 times per day. The urine was tested quantitatively daily for sugar and protein, if any. The urine was tested daily by Legals reaction and, if positive, by Gerhardts reaction too.

None of the cases included in this series was known to suffer from cancer or tuberculosis. In case of fever the patients were excluded from the material.

Some of the patients with renal disease may have had infectious processes of the urinary tract or the kidneys, but it is impossible with certainty to exclude infectious processes in the chronic renal lesion of patients with long-standing diabetes.

Group I: A control-group made up of non-diabetics in good health, 4 males and 6 females. Their ages ranged from 17 to 46 with an average of 32 years.

Group II: Diabetics without demonstrable vascular lesions. This group was made up of 37 patients, 16 male and 21 female diabetics. Their ages ranged from 12 to 64 years with an average of 33 years.

They were divided into subgroups depending on the duration of diabetes.

a. The known duration of diabetes less than two years:
   5 females, their ages averaged 34 years;
   6 males, their ages averaged 43 years.
   8 of these patients did not receive insulin on admission; all except two were discharged with insulin.

b. The known duration of diabetes 2—4 years:
   6 females, their ages averaged 39 years
   5 males, their ages averaged 21 years;
   One patient admitted without insulin, all of them discharged with insulin.

c. The known duration of diabetes 5 to 30 years, on an average 13.3 years:
   10 females, their ages averaged 36 years;
   5 males, their ages averaged 32 years.
   Two of these patients did not receive insulin, all except one discharged with insulin.

Group III: 8 diabetics with non-proliferative retinopathy and without renal disease:
1 female, 27 years old;
7 males, their ages varying from 22 to 65 years with an average of 52 years.
The known duration of diabetes was 0 to 20 years, on an average 12 years. All patients treated with insulin.

Group IV: 19 diabetics with renal disease and without proliferative retinopathy. Retinopathy was demonstrable in 16 out of 19 patients.
8 females, their ages varying from 28 to 69 years with an average of 53 years;
11 males, their ages varying from 22 to 64 years with an average of 37 years.
The known duration of diabetes was 7 to 26 years with an average of 16.5 years. All patients treated with insulin.

Group V: 15 diabetics with renal disease and proliferative retinopathy:
8 females, their ages varying from 19 to 52 with an average of 35 years;
7 males, their ages varying from 23 to 47 with an average of 34 years.
The known duration of diabetes was 14 to 25 with an average of 20 years. All patients treated with insulin.

In addition, in the eighth column of the graphical presentation of the results the values for two non-diabetic patients with chronic renal insufficiency with elevated blood urea are given.

METHODS

Protein is measured by the Kjeldahl method described by Andersen and Norman Jensen (1925—26).

Serum is fractionated in a *globulin* and *albumen part* with ammonium sulphate according to Henriques and Klausen (1932).

The non-glucosamine carbohydrate bound to protein is analysed by the orcinol method (Sørensen and Haugaard (1933), Rimington 1940). Known solutions of glucose are used as standards.

Glucosamine is analysed partly as described by M. Sørensen (1938). Experiments have shown that it is advantageous to treat the samples with acethyl-acetone reagent in 60 minutes instead of 20 minutes (Blix 1948).

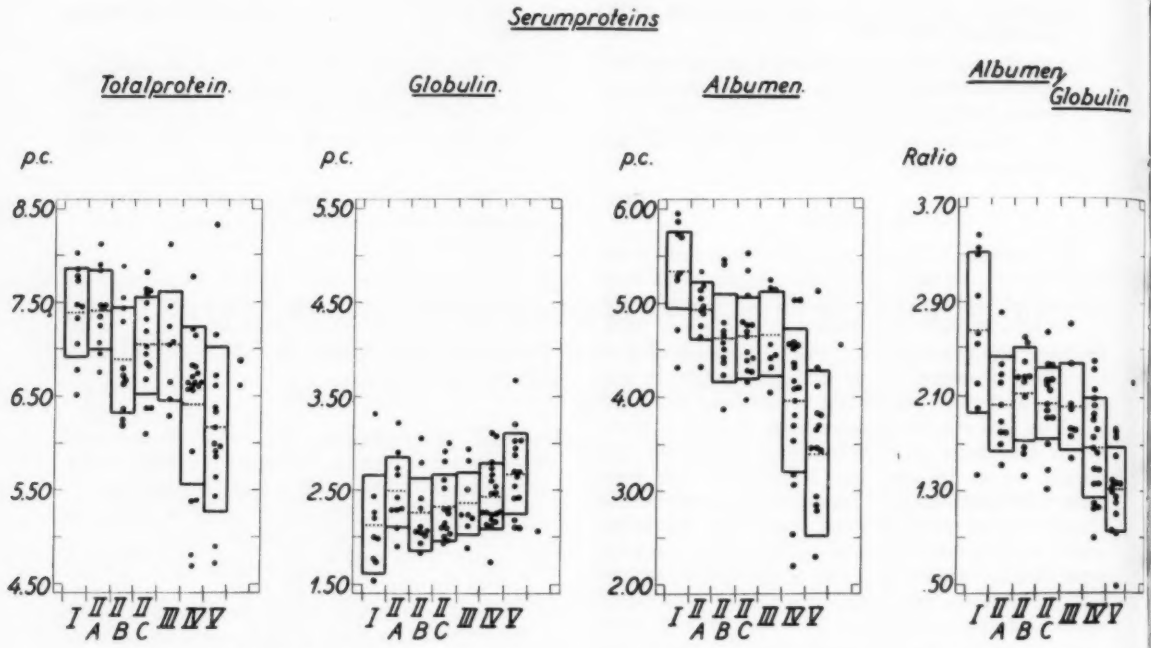


Fig. 1.

I: non-diabetic group.
II A: uncomplicated diabetic patients with duration of diabetes up to 2 years.
II B: uncomplicated diabetic patients with duration of diabetes 2—4 years.
II C: uncomplicated diabetic patients with duration of diabetes 5—30 years.
III: diabetic patients with non-proliferative retinopathy and without renal disease.
IV: diabetic patients with renal disease and without proliferative retinopathy.
V: diabetic patients with renal disease and proliferative retinopathy.
In the eighth column are given the results for two non-diabetic patients with uremia.

The broken lines indicate the means. The framed areas enclose the means ± S. D.

RESULTS

The values of total protein, globulin and albumen are given in figure 1. A decrease in the concentration of total protein is found in the groups with renal as well as retinal complications corresponding to the degree of the lesion.

In the uncomplicated group II a b c and group III no significant change is observed. The decrease of total protein is due to the lower amount of albumen, whereas the globulin concentration shows a tendency to increase in the two severely complicated groups. Of course the albumen-globulin ratio furthermore demonstrates the above mentioned changes.

The values of non-glucosamine protein-bound carbohydrate are given in figure 2.

The mean values for the non-diabetic group and for group II are almost the same and uninfluenced of the known duration of diabetes.

In the groups III—IV—V an increase in the amount of carbohydrate and especially the percentage of carbohydrate of total protein is observed. The differences between the alcohol and trichloracetic acid precipitates are greater than in the non-diabetic group.

Figure 3 reveals the findings of the carbohydrate in the ammonium sulphate fractionated proteins. It is obvious that the most remarkable rise of carbohydrate is found in the albumen part in spite of the decreased concentration in serum. The percentage of carbohydrate in the albumen part is distinctly elevated in the groups with vascular complications.

Within group II there is a tendency to elevated values of carbohydrate of albumen in the subgroup with the longest duration.

The slight rise of carbohydrate in the globulin part is due to an increase of this protein fraction, the percentage of carbohydrate of globulin is the same in all groups of patients.

Figure 4 gives the results of the glucosamine estimations. The number of patients examined in this way is too small to be divided into more than 3 groups:

1. non-diabetic controls without kidney lesions
2. uncomplicated diabetics and
3. diabetics with vascular lesions of the eyes and/or the kidneys.

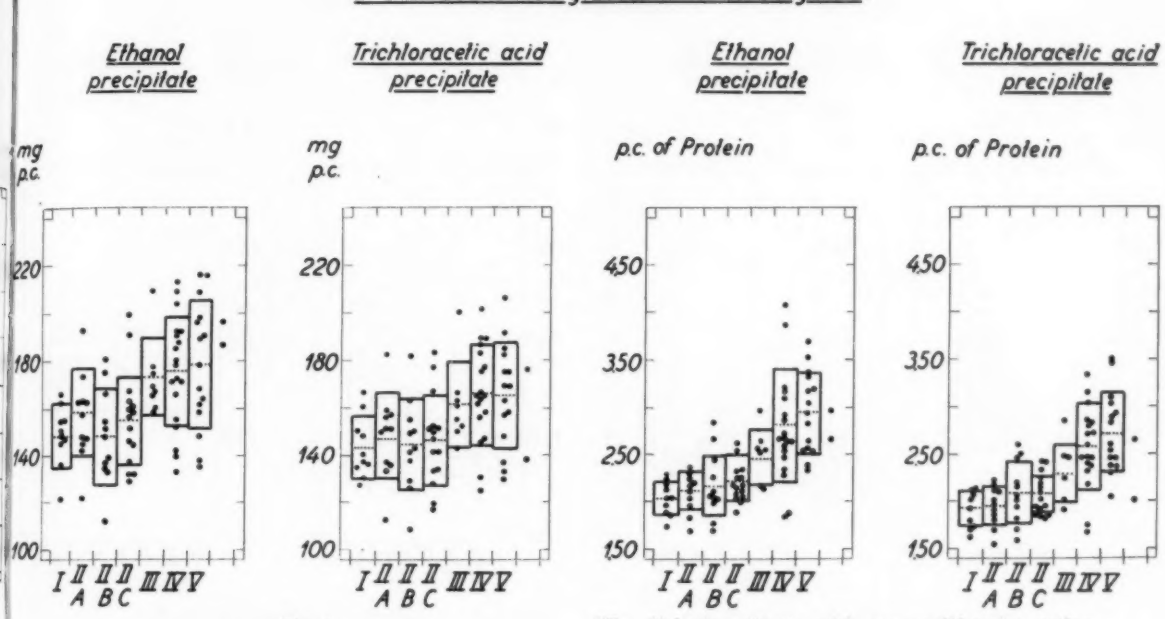


Fig. 2.

I: non-diabetic group.
II A: uncomplicated diabetic patients with duration of diabetes up to 2 years.
II B: uncomplicated diabetic patients with duration of diabetes 2—4 years.
II C: uncomplicated diabetic patients with duration of diabetes 5—30 years.
III: diabetic patients with non-proliferative retinopathy and without renal disease.
IV: diabetic patients with renal disease and without proliferative retinopathy.
V: diabetic patients with renal disease and proliferative retinopathy.
In the eighth column are given the results for two non-diabetic patients with uremia.

The broken lines indicate the means. The framed areas enclose the means ± S. D.

A slight increase of glucosamine is observed in the total serum protein of the diabetics. In the albumen fraction there is the same total amount indicating a higher percentage of glucosamine of the albumen part in the complicated groups. In the globulin fraction the percentage of glucosamine is the same in all three groups.

Table I reveals the findings in patients with elevated blood urea (> 50 mg per cent urea). Total protein and albumen are even more reduced than in group V with renal lesion and proliferative retinopathy. Seven of the patients in this group had proliferative retinal changes. Seven patients had edema.

As regards to the protein-bound carbohydrate the values are the highest observed in this material.

The difference between the carbohydrate-contents of the precipitates with ethanol and trichloracetic acid is higher than in any other group.

Table I.
14 diabetics with elevated blood urea
(> 50 mg per cent urea).

	Protein per cent		Non-glucosamine carbohydrate				Glucosamine (only 6 patients)	
			mg per cent		percentage of protein		mg per cent	percentage of protein
	mean	S. D.	mean	S. D.	mean	S. D.	mean	mean
Ethanol precip.	5.88	0.71	179	24.3	3.07	0.51	122	2.27
Trichloracetic acid precip.			167	21.8	2.83	0.39		
Albumen part	3.18	0.70	78.6	12.4	2.58	0.68	46.5	1.64
Globulin	2.70	0.44	84.6	13.4	3.17	0.48	73.1	2.83

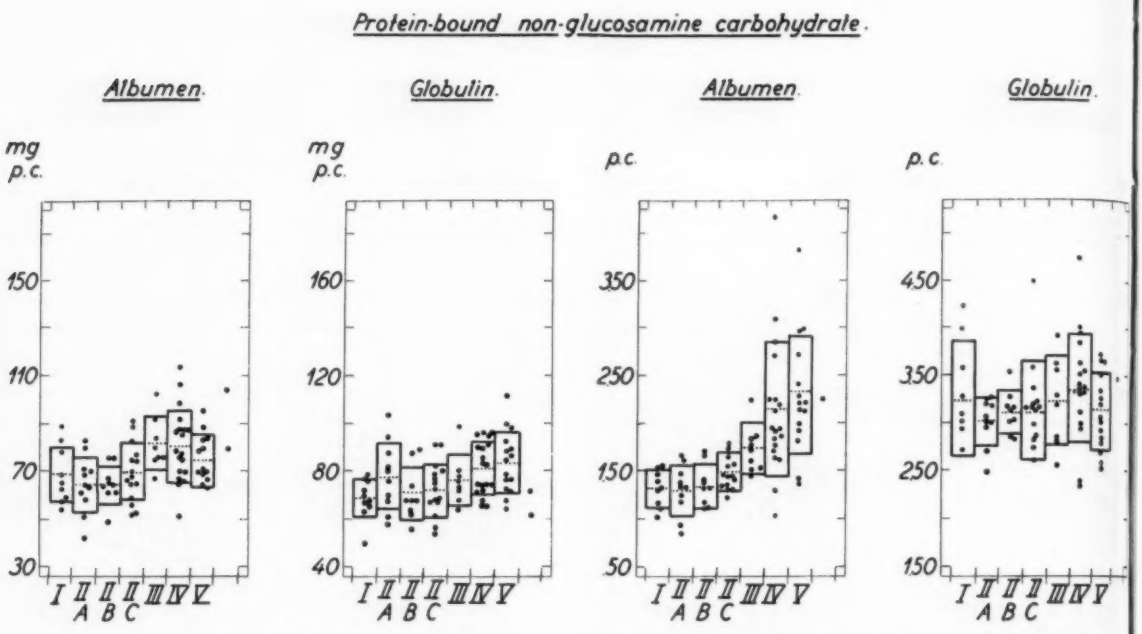


Fig. 3.

I: non-diabetic group.
II A: uncomplicated diabetic patients with duration of diabetes up to 2 years.
II B: uncomplicated diabetic patients with duration of diabetes 2—4 years.
II C: uncomplicated diabetic patients with duration of diabetes 5—30 years.
III: diabetic patients with non-proliferative retinopathy and without renal disease.
IV: diabetic patients with renal disease and without proliferative retinopathy.
V: diabetic patients with renal disease and proliferative retinopathy.
In the eighth column are given the results for two non-diabetic patients with uremia.

The broken lines indicate the means. The framed areas enclose the means ± S. D.

Figure 5—6—7 give the results of repeated examinations of the serum-proteins after a period of treatment in the hospital.

Almost all patients were badly controlled before the treatment, and all of them obtained good control during the observation period.

Two groups are analysed. The first group (8 patients) includes complicated diabetics, the second one non-complicated diabetics (6 patients). In both groups the non-glucosamine carbohydrate values in total protein were more than 165 mg per cent.

During the treatment the complicated group shows in all cases a trend towards the normal ranges regarding total-protein, albumen and carbohydrate and the percentage of carbohydrate of the proteins.

The treatment-period was in this group from 4 to 30 days, on an average 15 days.

The uncomplicated group does not demonstrate a uniform amelioration of the protein patterns; the initial changes differed less from the normal protein-amounts and carbohydrate per cents in this group than in the first group, but roughly estimated a tendency towards normal values was observed.

The period of treatment was from 6 to 28 days, on an average 15 days.

DISCUSSION

It is a well-known clinical observation that the badly controlled diabetic may have a negative nitrogen balance, but the influence of diabetes on plasma-proteins is rather seldom investigated.

The total proteins of plasma can be satisfactorily estimated by precipitation and measurement of the nitrogen according to K j e l d a h l.

The fractionation by ammonium sulphate, however, is known to give very inhomogeneous precipitates as discussed by G u t m a n (1948).

The precipitate gained by 50 per cent saturation with ammonium sulphate is mainly made up of β- an γ-globulins. The supernatant fluid contains albumin, serummucoid and some α-globulin. The fractionation used in this study therefore only gives a rough picture of the changes of the different protein fractions.

By electrophoretic studies on plasma proteins from diabetics S c h n e i d e r, L e w i s, and M c G u l l a c h (1948) frequently found abnormal protein patterns.

The typical changes in unadequately treated patients were a reduced level of albumin and an

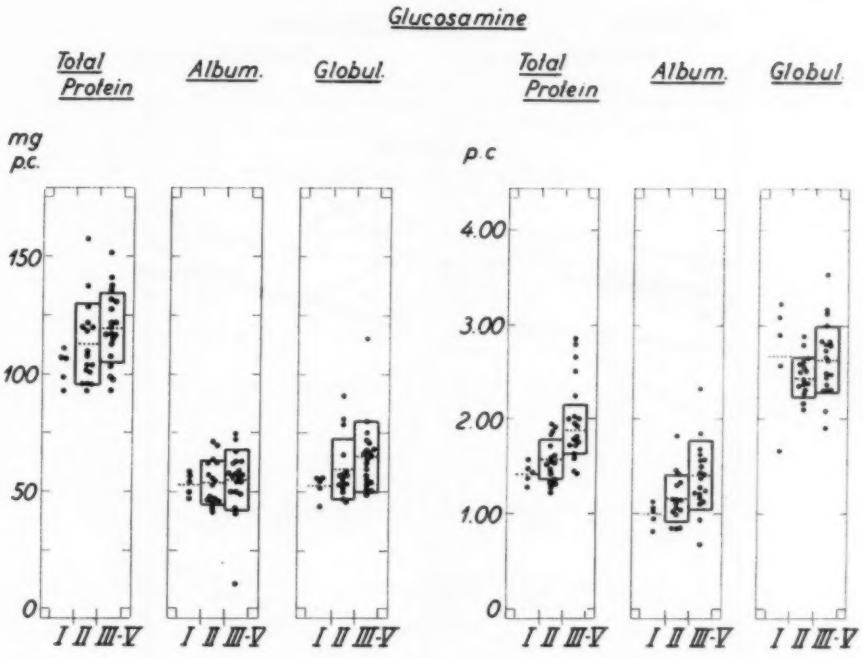


Fig. 4.
I: non-diabetic control group.
II: uncomplicated diabetic patients.
III—V: diabetic patients with vascular lesions of the eyes and/or the kidneys.
The broken lines indicate the means. The framed areas enclose the means ± S. D.

increase in β-globulin. The total quantity of protein might be normal or only slightly reduced.

If no complications were present the plasma proteins could be restored by adequate treatment. In case of complications as infection, renal insufficiency or retinopathy the restoration of the plasma protein levels to normal was brought about with much more difficulty.

Rifkin and Petermann (1952) examined electrophoretically serum and urinary proteins in 10 diabetics with glomerulosclerosis. The sera from all patients revealed a decrease in albumin, with a marked elevation of the α-2 globulin. α-1 and γ-globulin were within the normal range and the β-globulins were either within normal limits or slightly elevated.

Our diabetics without complications had a mean value of total protein a little below the mean value for the non-diabetics. Also the albumen part is insignificantly lower in the uncomplicated diabetics.

In group III—IV—V the changes are more obvious. The mean values of total protein and of albumen are markedly reduced—especially in the groups with the most severe degree of complications.

All patients in the two groups examined on admission and at the discharge were unsatisfactorily controlled at the first examination. None of the patients had acidosis. During their stay in the hospital they all obtained better control of the diabetes. The diet used contained about one gram of protein per kg bodyweight.

The measurements of protein-bound carbohydrates reveal abnormal values. Increased values are observed in the complicated groups—also in the group without renal involvement. The percentage of carbohydrate bound to protein is increasing with the severeness of the degree of complications. Especially distinct elevations are observed in the albumen-part. This fraction contains—besides the carbohydrate free albumin—some globulin and serum-mucoid, which are the protein-fractions containing the highest percentage of carbohydrate.

Seibert, Pfaff, and Seibert (1948) have measured the carbohydrate-contents of different fractions of plasma proteins obtained by fractionation according to Cohn. They found in α-2 globulin up to 5.83 per cent carbohydrate (Fraction IV 6).

Also serummucoid is present in our albumen part. Weimer, Mehl, and Winzler (1950) analysed a crystalline serummucoid from human plasma and found 16.4 per cent hexoses and 11.9 per cent hexosamine.

Serummucoid is precipitated by ethanol, but only to a slight degree, or not at all, by trichloracetic acid.

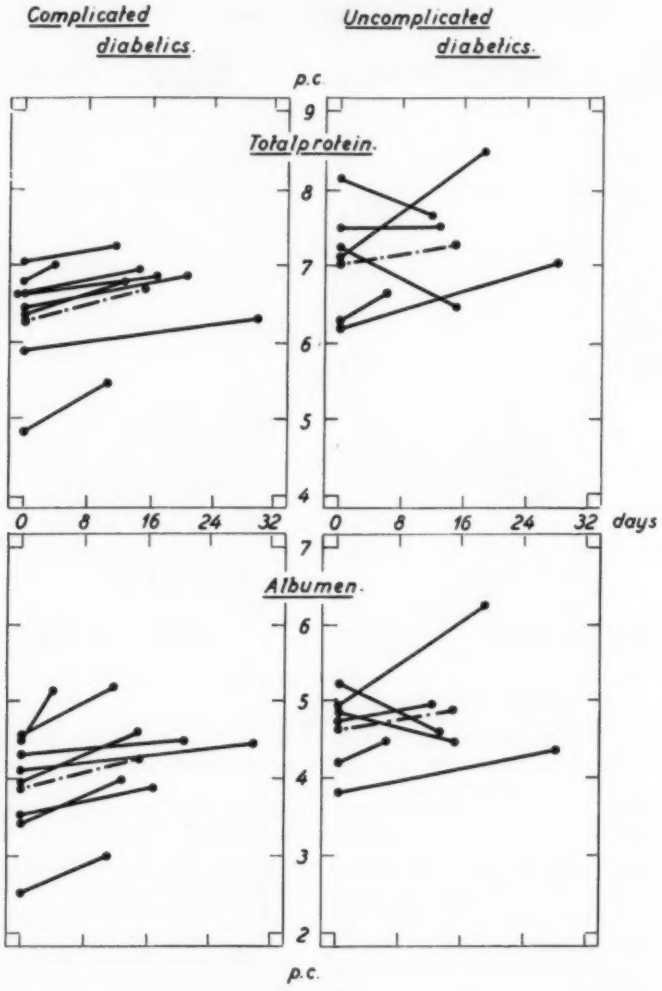


Fig. 5.
The broken lines indicate the mean change.

The difference between the carbohydrate contents of the ethanol and the trichloracetic acid precipitates may therefore stand mainly for the amount of serummucoid.

The difference between the amounts of carbohydrate between the two precipitates from some sera is also increasing according to the degree of the severeness of the complications. In the uremic group in our material the difference is about 19 mg per cent and comparable with the results of Berkman, Rifkin, and Ross (1953) who found an average of 18.3 mg per cent carbohydrate in their serummucoid precipitate obtained by special precipitation of serum from diabetics with renal involvement.

We did not succeed in finding a correlation between the protein-bound carbohydrates and the blood-sugar concentration at the moment when the blood samples were taken. Neither did we find a correlation between the sugar excretion in the urine the preceding 2 to 3 days and the protein-bound carbohydrates. Only uncomplicated cases were used for this evaluation.

As mentioned introductorily, increased levels of serum protein-bound carbohydrates are found in highly different types of diseases such as infections, cancer and vascular lesions. Berkman, Rifkin, and Ross (1953) reported non-diabetic patients with renal disease with highly increased values of both non-glucosamine protein-bound carbohydrate and glucosamine.

The reported changes of plasma proteins in diabetics must therefore at present be considered to be the result of an unspecific reaction of the organism unless a more refined technique should allow an isolation of speciel glycoproteins in diabetics.

The repeated examinations of the plasma pro-

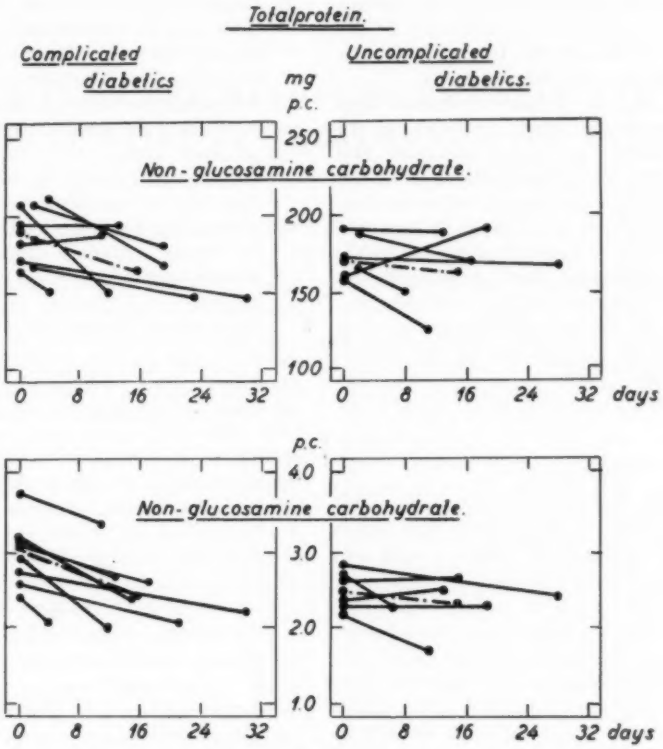


Fig. 6.
The broken lines indicate the mean change.

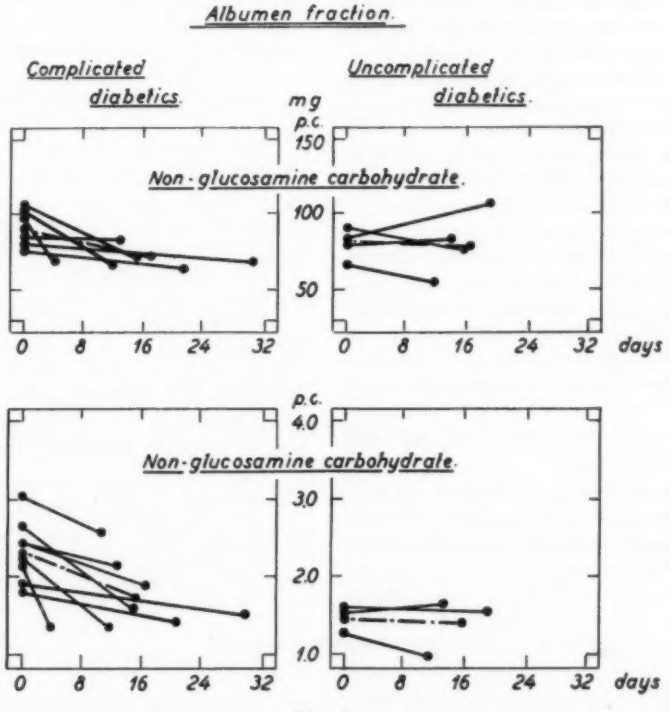


Fig. 7.
The broken lines indicate the mean change.

teins in diabetics with elevated values of protein-bound carbohydrates showed a tendency to re-establish normal levels of the total-protein, albumen and protein-bound carbohydrates.

Whether these changes reflect a similar normalizing tendency in the tissue proteins we do not know, but it does not seem unlikely. The modern concept of a dynamic equilibrium of the body proteins and the interchange between plasma proteins and cellular proteins may support this suggestion. (P o l l a c k and H a l p e r n 1951).

Often we have observed that proteinuria recently discovered in long-standing diabetes disappears after 3—6 weeks confinement to bed under due control of the changes of the retinopathy, but it is our "clinical feeling" that this lesion not infrequently ameliorates under the same treatment.

SUMMARY

1. Serum proteins, measured as total-protein and after fractionation by 50 per cent ammonium sulphate, are examined in diabetics with and without demonstrable vascular lesions.

   Insignificantly lowered values of total-protein and albumen fraction were observed in the non-complicated groups. Reduced values of total-protein and albumen fraction were found in the complicated groups and the deviations were roughly concomitant with the degree of the lesions.

2. Protein-bound carbohydrate was estimated by orcinol in the same groups. Normal values were found in the uncomplicated groups regardless of the duration of diabetes.

   Increased values of protein-bound carbohydrate were found in the complicated groups. The total amount and especially the percentage of carbohydrate of the albumen part were increased concomitantly with the degrees of the vascular renal lesions.

   The percentage of carbohydrate of globulin was almost uniform in the different groups.

3. Serum-protein bound glucosamine was estimated in an uncomplicated and a complicated group of diabetics. Elevated values were observed in the complicated group and especially in the percentage of glucosamine of albumen.

   The uncomplicated group showed only slightly elevated values.

4. A uremic group of patients showed the most abnormal values of total-protein, albumen, protein-bound carbohydrate and glucosamine observed in these series.

5. Repeated examinations of patients during their stay in the hospital revealed a tendency toward normalization of abnormal values of total-protein, albumen, and protein-bound carbohydrate during the treatment. These findings were marked and uniform in a complicated group, less impressive in an uncomplicated group in which the deviations from the normal levels were less pronounced.

6. The results are compared with similar changes in highly different diseases and it is concluded that the observed changes of the serum protein in diabetics with vascular lesions must be considered as non-specific.

The present investigations have been published in detail in Reports of the Steno Memorial Hospital and the Nordisk Insulinlaboratorium. 1953, *5:* 71.

References:

1) *Andersen, A. C.* and *B. Norman Jensen:* Ztschr. f. analyt. Chemie. 1925—26, *67:* 427—448.
2) *Berkman, J., H. Rifkin,* and *G. Ross:* J. Lab. and Clin. Med. 1953, *40:* 415—421.
3) *Blix, G.:* Acta Chem. Scandinav. 1948, *2:* 467—473.
4) *Greenspan, E., I. Lehman, M. M. Graff,* and *E. B. Schoenbach:* Cancer 1951, *4:* 972—983.
5) *Gutman, A. B.:* Advances in Protein Chemistry 1948, *4:* 155—200.
6) *Henriques, V.* and *U. Klausen:* Bioch. Ztschr. 1932, *254:* 414—433.
7) *Immers, J.* and *E. Vasseur:* Acta Chem. Scandinav. 1952, *6:* 363—375.
8) *Israel, H. L., M. B. Webster,* and *I. E. Maher:* Am. J. Med. 1949, *6:* 745—750.
9) *Jacobs, H. R.:* J. Lab. and Clin. Med. 1949, *34:* 116—122.
10) *Keiding, N. R.:* In press. 1953.
11) *Pollack, H.* and *S. L. Halpern:* Advances in Protein Chemistry 1951, *6:* 383—453.
12) *Rifkin, H.* and *M. L. Petermann:* Diabetes 1952, *1:* 28—32.
13) *Rimington, C.:* Bioch. J. 1940, *34:* 931—939.
14) *Schneider, R. W., L. A. Lewis,* and *E. P. McGullagh:* Am. J. Med. Sci. 1946, *212:* 462—465.
15) *Seibert, F. B., M. L. Pfaff,* and *M. V. Seibert:* Arch. Biochem. 1948, *18:* 279—295.
16) *Simkim, B., H. C. Bergman,* and *M. Prinzmetal:* Am. J. Med. 1949, *6:* 734—744.
17) *Stary, Z., Ö. Kaleoglu,* and *F. Bursa:* Istanbul contributions to Clinical Science 1951, *1:* 311—321.
18) *Sørensen, M.:* Meddelelser fra Carlsberg Lab. 1938, *22:* 387—493.
19) *Sørensen, M.,* and *G. Haugaard:* Bioch. Ztschr. 1933, *260:* 247—277.
20) *Weimer, H. E., J. W. Mehl,* and *R. J. Winzler:* J. Biol. Chem. 1950, *185:* 561—568.

MONILIASIS OF THE MUCOUS MEMBRANES AND LUNGS AS A COMPLICATION OF TREATMENT WITH ANTIBIOTICS CORTICOTROPIN AND CORTISONE

By HARRIET BRATLUND and C. HOLTEN

The fungus Candida albicans has been recognized for many years as the cause of local infections (»thrush«) in the oral cavity and vagina, of paronychiae and of more or less extensive skin affections. These infections have previously shown little tendency to spread and only extremely seldom have they been fatal. They most frequently occurred in enfeebled, emaciated infants. In adults it was only encountered in the final stages of chronic tuberculosis and other cachectic states.

Since 1945, however, an increasing number of reports from all parts of the world have been published concerning cases where Candida albicans has caused more extensive disease, also in adults who have not been debilitated.

Candida albicans is quite often found on the mucous membranes as a saprophyte. The intact mucous membrane does normally neither permit Candida albicans to grow among the epithelial cells nor to penetrate into the underlying tissues, and even a lesion of the mucous membrane does usually not create the possibility for the fungi to extend into the deeper layers and produce disease.

Candida albicans may however, become virulent if the tissue resistance has become lowered for some reason or other (insufficient nutrition, wasting diseases, hormonal deficiency or imbalance etc.), or when the fungi are present in very great quantities. This may occur when other micro-organisms have been suppressed by treatment with antibiotics, the fungi being resistant to all commonly used antibiotics.

Under such conditions the white spots well known from the thrush of children may appear more or less extensively, depending on the conditions for growth. As a rule, these spots disappear in the course of 3—4 days, but under particularly unfavourable conditions, they may persist for months, extend over, and in some cases, penetrate the mucous membranes, spread into the submucosa and eventually into the vessels. In this way, the basis for metastatic processes in various organs may be established. The condition for this is that the mycelium and spores are not killed in the blood or tissue fluids, i. e. absence of antibodies and potent phagocytes.

For the various forms of disease caused by Candida albicans the term moniliasis is generally used.

Although complete unanimity does not prevail on this point, the general trend of the literature is that the increasing use of antibiotics is the main cause of the increasing incidence of moniliasis and of the fact that adults are affected quite frequently. In reviewing the cases from the literature it is obvious that the majority of the patients have been given more than one antibiotic. The patients concerned were generally seriously ill due to various pyrexial conditions, which frequently turned out to be blood diseases of one type or another. The condition was uninfluenced by the antibiotics employed for which reason one antibiotic after another was given or several were administered simultaneously. Cases have, however, also been reported in which a primary infection was correctly diagnosed and antibiotic therapy was undertaken in accordance with the sensitivity of the bacteria. For instance O r m e r o d & F r i e d m a n n treated a case of maxillary sinuitis caused by staphylococci with penicillin, streptomycin and aureomycin. Although the patient was an otherwise healthy woman of 49 years, a cavernous pulmonary condition, apparently caused by Candida albicans, developed.

It is a general assumption that administration of Corticotropin and Cortisone diminishes the resistance against infections, in any case when fairly large doses are involved. The mechanism of this lowering of resistance is not adequately elucidated but it seems reasonable to presume that at least partly a reduction of resistance may be an effect of the same factors which are responsible for the weakened reaction (as regards pyrexia, pain etc.) to infections, a phenomenon frequently observed on administration of these hormones.

THE AUTHORS' PERSONAL OBSERVATIONS

In Department C of the University Medical Clinic, Aarhus Municipal Hospital, we have observed cases af moniliasis in patients who, in addition to antibiotics, received Corticotropin and/or Cortisone as well as cases in which no antibiotics were administered, but only ACTH or Cortisone or both.

In the first cases of moniliasis which were encountered, none of which were very extensive,

From Department C, the University Medical Clinic, the Municipal Hospital, Aarhus, Denmark.

we were content to observe the presence of the characteristic white detachable spots on the mucous membranes. As gradually more cases accumulated and among these some severe and extensive affections, it became essential to confirm the diagnosis by laboratory examinations. Scrapings from the spots were therefore examined microscopically and, in addition, cultures from the spots, sputum etc. were undertaken. At the beginning, cultures were examined at the Serum Institute, Copenhagen, later at the University Institute of General Pathology in Aarhus.

An account will be given of cases of moniliasis, some of which were extremely severe. We are unable to estimate the incidence of moniliasis among patients treated with antibiotics (without ACTH and/or Cortisone). However, it is certain that no severe cases were encountered in such patients during the years in which antibiotics have been employed liberally.

We have, however, been able to trace all cases of moniliasis which have occurred in patients treated with ACTH and Cortisone even if the attack was only slight, as the records of all patients treated with these hormones are kept in a special register. When the cases of moniliasis had been severe or moderately severe by virtue of prolonged duration, extent or serious complications, the fungus infection had of course been expressedly recorded as a part of the combined diagnosis.

The incidence of moniliasis in patients treated with ACTH and/or Cortisone could therefore be recorded. From the date when these hormones were first employed as routine treatment (March 1950) until the present account was written (February 1954), approximately 210 patients suffering from various diseases have been treated. Patients to whom treatment was only administered for a few days (7 days or less) were omitted. Among these 210 patients, 18 cases of moniliasis were observed.

Table 1.
Incidence of Moniliasis in three Different Groups.

	Slight	Moderate	Severe	Total	
ACTH-Cortisone	4	2	2	8	(103)
ACTH-Cortisone +antibiotics	4	2	1	7	(107)
Solely antibiotics	3	—	—	3	

Table 1. The figures in brackets in the last column indicate total number of patients who received ACTH/Cortisone and no antibiotics and the number of patients in this group (see text) who in addition received antibiotics.

Of these 18 patients (see Table 1), *8 received hormone treatment alone*, i. e. no antibiotics, at the time when the spots were discovered nor were antibiotics administered during a period of at least 10 days prior to the observation of the moniliasis infection.

In 7 *patients, hormones and antibiotic therapy were administered simultaneously.* Included in this group is, however, one patient suffering from rheumatoid arthritis and pyelonephritic contracted kidney who had received hormone treatment for a prolonged period and was still receiving it, and who had been given aureomycin for a week. Aureomycin had been discontinued for 4 days when moderate moniliasis infection in the mouth and pharynx was observed. In addition, a patient with a severe blood dyscrasia (following gold therapy) is included. This patient had received ACTH for 61 days and this treatment was discontinued 5 days before moniliasis was first observed. This patient had previously received antibiotic therapy with terramycin and penicillin and at the time when the moniliasis was observed, chloromycetin was administered.

In these 7 cases, the *following antibiotics were involved:*

aureomycin: 1 (slight)
aureomycin + penicillin: 1 (slight)
penicillin: 1 (slight)
penicillin + streptomycin: 1 (moderate)
penicillin + terramycin + penicillin: 1 (moderate)
penicillin + terramycin + chloromycetin: 1 (severe)
chloromycetin: 1 (slight).

3 cases concern patients in whom treatment with antibiotics alone can probably be regarded as the cause of the development of moniliasis. These patients had admittedly received ACTH-Cortisone treatment but this treatment had been discontinued 2½ months, 25 days and 3 weeks, respectively, before signs of moniliasis were observed; all 3 cases were slight.

The *antibiotics administered* to these patients were:

chloromycetin: 2 (slight)
penicillin: 1 (slight).

The *primary conditions present* in the 18 patients were:

ACTH/Cortisone alone:

1—3) Rheumatoid arthritis: 2 (slight) and 1 complicated by cardiospasm. Severe moniliasis +.
4) Bronchial asthma: 1 (slight).
5) Leukaemic erythrodermia: 1 (slight).
6) Periarteriitis nodosa: 1 (moderate) +.
7) Lipoid nephrosis: 1 (moderate).
8) Ulcerative colitis: 1 (severe) +.

ACTH/Cortisone + antibiotics:

1) Severe blood dyscrasia: 1 (severe).
2) Rheumatic carditis: 1 (slight) +.
3) Rheumatoid arthritis: 1 (moderate) +.
Acute enterocolitis. Sepsis. Acute Delirium.

4) Rheumatoid arthritis: 1 (moderate) +.
5) Rheumatoid arthritis. Pleuropneumonia: 1 (slight).
6) Hepatic cirrhosis: 1 (slight) +.
7) Benign lymphogranulomatosis: 1 (slight).

Antibiotics solely:
1) Aleukaemic leukaemia: 1 (slight) +.
2) Rheumatoid arthritis: 1 (slight).
3) Rheumatoid arthritis: 1 (slight). Coronary occlusion. Duodenal ulcer and melaena.

The cases marked + have died, totalling 8. In the case of one patient (suffering from ulcerative colitis) the cause of death was suicide and death occurred one year after the infection with moniliasis had disappeared. In the case of six patients, (1 periarteriitis nodosa, 1 rheumatic carditis, 1 rheumatoid arthritis and chronic pyelonephritis, 1 hepatic cirrhosis, 1 aleukaemic leukaemia and 1 case of rheumatoid arthritis with acute sepsis and acute delirium) it can safely be stated that the moniliasis was of no significance for the final issue. Hence, only in one patient can the infection with monilia be assumed to have contributed to the fatal issue. This, however, does not mean that the moniliasis in the rest of the cases was not serious and troublesome; in fact, in at least 2 others this complication made the issue doubtful for quite a long time.

The incidence of moniliasis in the group of patients concerned, all of whom were treated with ACTH/Cortisone, may be stated as 8—10 per cent. The incidence among patients treated with ACTH/Cortisone alone appears from Table 1, viz. 8 out of 103 cases. No definite difference in the incidence among these cases and among the cases which received both hormone and antibiotic therapy (10 out of 107 cases) has been demonstrated.

Further details will be given concerning the patient in whom a severe moniliasis complicated a case of rheumatoid arthritis treated with hormones, and who also had cardiospasm. In addition, the other 2 severe cases will be related in detail.

Case 1.

Female, aged 54 years. Admitted 28. IX. 53. Died 17. XII. 53.

Steadily progressing rheumatoid arthritis since 1929. Hyperthyroidism in 1939, treated with diiodotyrosine, cured after approximately one year.

Because of the activity of the rheumatoid arthritis which involved swelling and pain in several joints and the total incapacity of the patient due to this activity and the advanced, inveterated joint changes, ACTH therapy was instituted on 15. X. 53: 20 units x 3 (Acton).

Shortly before admission, X-ray examination of the oesophagus had been undertaken on account of periodic slight difficulty in swallowing and pressure behind the sternum at mealtimes. The diagnosis made was »curly oesophagus«. The examination was repeated on admission, revealing typical cardiospasm which, however, caused only very moderate symptoms.

On 27. X. 53, a generalized exanthema appeared with red spots and papules. As it appeared that this could not have been caused by barbiturates or similar drugs, Acton was suspected as an etiological factor. Corticotropin Organon (Nov. 12th) and, (on November 13th and 14th) ACTH from whale hypophyses was therefore administered. (The last mentioned preparation was procured through the kind help of the Danish Rheumatism Association from »Nyco«, Oslo). No change was observed in the exanthema. Two days after the appearance of the exanthema (29. X. 53) typical thrush spots appeared on the tongue, the inner surface of the cheeks and in the fauces.

Simultaneously with the appearance of this affection, the symptoms from the patient's cardiospasm became markedly intensified and constant regurgitation and salivation occurred. About a week after the initial symptoms, her voice became hoarse and on the following day aphonic. Her temperature rose. On November 16th, bilateral parotitis was observed. Typical thrush membranes in the larynx were seen. The infection with moniliasis was treated by gargling with sodium bicarbonate solution and parenterally she was given vitamin B preparation (Becoplex, Ferrosan Ltd.). For a long period the patient was in poor condition. Gradually, the moniliasis improved, however, and on November 23rd it had almost disappeared. Corticotropin therapy was discontinued on November 15th. On December 9th the patient was allowed up (sitting). From December 14th walking exercises on a small scale were commenced but that day phlebitis developed in the left leg. The patient died suddenly on the following day with typical signs of embolism of the pulmonary artery.

Summary. Female, aged 54 years, with severe, still active rheumatoid arthritis of 24 years duration and mild cardiospasm was given ACTH therapy. 13 days after this had been started, generalized exanthema developed and 2 days later, typical moniliasis was observed in the mouth and pharynx. In connection with this, the cardiospasm deteriorated rapidly, aphonia was present for some days and laryngeal moniliasis and bilateral parotitis developed. The moniliasis infection improved slowly. Phlebitis in the left leg developed. Death from pulmonary embolism.

There can be no doubt that in this case, the hormone therapy conditioned the development of the moniliasis and that this caused the cardiospasm to deteriorate. This led to a serious impairment of nutrition and increasing weakness which in connection with her immobility, caused a thrombophlebitis. Pulmonary embolism was the immediate cause of death. The exanthema

observed may be interpreted as allergically conditioned by the infection with moniliasis. The white blood cell count was not estimated at the time of the skin eruption. It seems beyond doubt that the moniliasis increased the patients debility in this case.

Case 2.

Male, aged 57 years. Ulcerative colitis. Admitted 18. VI—6. XII. 52.

Ulcerative colitis since 1944 with periodic remissions. Admitted in poor condition with numerous loose, bloody stools. Diet and tannic acid enemata. From 28. VI—20. VII. 52 he had phthalylsulphathiazole 1 gm. x 4 and from 12. VII.—20. VII. 52 streptomycin in addition. From 26. VII. 52 ACTH (Acton) 10 units x 3. On 12. VIII. 52, i. e. 23 days after the discontinuation of all antibiotic therapy, typical spots on the tongue, in the mouth and fauces occurred. The spots coalesced and spread to the pharynx and hypopharynx and on 3. X. 52 to the larynx, and his voice became aphonic. By treatment with a vitamin B preparation (Becothimin, Ferrosan Ltd.) intramuscularly and ascorbic acid intravenously together with local application of neosalvarsan glycerol, the moniliasis improved slowly. By 31. X. 52 it had completely disappeared.

The case was further complicated, in the middle of September 1952, by an abscess in the gluteal region following ACTH injections; Candida albicans was not found in the pus from this abscess.

Summary: Male, aged 57 years, with severe ulcerative colitis; antibiotic therapy: phthalylsulphathiazole for 24 days, the same and streptomycin for 9 days. 6 days after the discontinuation of antibiotic therapy, ACTH treatment was instituted. Following 16—17 days of this treatment, moniliasis infection developed in the oral cavity and spread to the pharynx and larynx. The moniliasis did not occur till 3 weeks after the discontinuation of antibiotic therapy. It is improbable that the antibiotic therapy had any important significance for the development of the moniliasis infection; the hormone treatment, naturally in connexion with the severe primary disease, must have been the decisive factor.

Case 3.

Male, aged 70 years: (rheumatoid arthritis), haematemesis, melaena, severe toxic thrombopenia, acute haemorrhagic anaemia, moniliasis.

The patient was admitted 15. IX. 53 with melaena. Anaemia (Hb. 40 per cent.) and thrombopenia (1,700) was found, W. B. C. was 3,600 with 62 per cent. granulocytes. Recurrent severe melaena during the period 15.—20. IX. 53; several transfusions were given.

Treatment with ACTH was instituted: 20 units x 3 from 21. IX.—21. XI. 53. The thrombopenia improved considerably as did the anaemia. The granulocyte count became completely normal.

From 1. XI. 53 the patient complained of dryness in the mouth. On 9. XI. 53 signs of infiltration in lower lobe of the left lung. From 9. XI. 53 to 14. XI. 53 terramycin, following this penicillin until 21. XI. 53 and chloromycetin from 21. XI. 53 to 30. XI. 53. Not until 14. XI. 53 did the patient become pyrexial.

A couple of days after the commencement of chloromycetin therapy, characteristic white spots in the mucous membrane of the mouth were observed. These spread rapidly and on November 26th the voice became aphonic. On 3. XII. 53 thick white membranes were found in the larynx and far down in the trachea (Professor H. C. Andersen).

The pulmonary condition took a singularly torpid course: there was no immediate pyrexia; moderate pyrexia developed for a short period after 5 days. From 9. XI.—17. XI. 53 the sputum was very scanty but on 17. XI. 53, 8—10 large, brownish-red lumps were expectorated and simultaneously the temperature rose further. The expectoration continued for 2—3 weeks and then diminished gradually. The pyrexia disappeared after approximately one week. Candida albicans was demonstrated on direct microscopic examination of scrapings from the mouth and from the larynx. Sputum 4. XII. 53 showed Candida albicans (directly and on culture). X-ray examination 22. XII. 53: marked opacity of the upper third of the left lung; slight interlobar exudate. On 5. I. 54 the infiltration had regressed to a great extent.

Summary: Male, aged 70 years, admitted with melaena; very severe thrombopenia demonstrated. Moderate pyrexia ascribed to infection in the left lung indicated treatment with terramycin for 5 days. Diarrhoea occurred for which reason terramycin was substituted by penicillin but as this did not influence the temperature, penicillin was substituted by chloromycetin. Thrushlike spots in the mouth were not observed till 2—3 weeks after commencement of pyrexia but the patient had complained of feeling of dryness and irritation in the throat for about three weeks; whether this was a symptom of thrush (without spots) cannot be determined. The pulmonary condition changed character as regards sputum after the administration of terramycin and penicillin; the very scanty expectoration became copious and brownish-red. Penicillin was discontinued and chloromycetin given. Not until over a week after this, the typical affection in the mouth with spots in the pharynx was seen; aphonia developed a few days later.

Although ACTH treatment was discontinued 5 days prior to the appearance of manifest signs of moniliasis, principal responsibility should presumably be ascribed to the hormone treatment.

The affection of the mouth, pharynx, larynx and trachea can hardly be any other than moniliasis. The pulmonary condition as it manifested

itself after the sputum had changed (copious and strangely coloured sputum with Candida albicans on direct microscopic examination and on culture) and as it appeared on X-ray examination, can justly be presumed to be moniliasis. It may be assumed that an infection of ordinary bacterial nature first developed and that the Candida fungi thereafter spread, during antibiotic therapy, into the diseased lung tissue from the trachea where the fungi were present in the membranes. Admittedly there is a possibility that pulmonary moniliasis was present from the start and if this was the case, the antibiotic therapy could not have exerted any decisive influence as it was not started until the pulmonary signs became apparent; the former possibility seems, however, to be the most probable.

Moniliid.

In the severe, first case of the patient with rheumatoid arthritis and cardiospasm, it was mentioned that 2 days prior to the observation of thrush in the mouth, a spotty, papular generalized exanthema appeared. We are inclined to believe that this was a moniliid, an allergic exanthema produced by the metabolic products of Candida albicans. Such generalized allergic exanthemata in moniliasis of the mucous membranes have been described (cf. e. g. Andrews: Diseases of the Skin, Saunders, Philadelphia, 1949, pp. 295 ff.).

We have observed yet another case with quite a similar, generalized exanthema. This occurred in a female, aged 63 years, with lipoid nephrosis. ACTH 10 units × 3 was administered for 15 days, following which a generalized exanthema occurred. Simultaneously, moniliasis was observed in the oral cavity. The exanthema persisted for about a week, subsequently regressed and disappeared 10 days later. The moniliasis of the mucous membranes persisted longer, extended to the larynx (Candida albicans demonstrated) and disappeared after one month. In this case leucocytosis was found coincident with the exanthema: 21,000 white blood cells with 80 per cent granulocytes and 2 per cent eosinophils; 2 months after the outbreak and approximately one month after the disappearance of moniliasis, 11,000 leucocytes were still found; after another week the number of leucocytes was 8,300. Andrews (l. c.) mentioned leucocytosis as a characteristic sign in cases of moniliid.

Microbiological Diagnosis.

As mentioned previously, we were content in the very first cases with the confirmation of the presence of characteristic spots and membranes in the oral cavity and pharynx. Later, scrapings were taken from the spots for examination for the presence of fungi and finally we included cultures from the spots and membranes, sputum etc. for diagnosis.

Microscopic examination was not undertaken in 5 out of the 18 patients in this material, but in 12 typical Candida albicans was found in the scrapings.

In one case (the patient with hepatic cirrhosis which terminated fatally) where for 4 weeks an apparently slight moniliasis had been present in the mouth and pharynx, autopsy showed on microscopic examination isolated areas of peribronchial pneumonia with necrosis and in the centres of these in several places aggregations of fungi, which resembled Candida albicans, while no definite macroscopic abnormality was demonstrable. They appeared to be localized in the bronchial walls and extended from there slightly into the adjacent, partly necrotic tissue; there was an abundant infiltration with leucocytes and lymphocytes in the surroundings. This is apparently an example of metastatic moniliasis in an adult who was very debilitated; perhaps the hormone treatment, even if it was only of rather short duration, may have lowered the resistance of the tissues.

Cultures from scrapings from membranes in the oral cavity of 3 patients were performed; abundant growth of Candida albicans was obtained in all 3 cases. In a fourth (case 3) growth of Candida albicans was obtained from the scrapings from the oral cavity and larynx as well as from the sputum.

It is obvious, that the demonstration of Candida albicans on microscopical examination of scrapings from the affected mucous membrane, by direct microscopy of the sputum or on culture from these materials or by both methods does not suffice to establish the diagnosis of moniliasis. The presence of the fungi on mucous membranes, and particularly when these are injured, is too frequent for this. The diagnosis must primarily depend on the characteristic appearance of the affection observed: white or yellowish white, dry spots, scattered, frequently only 1 mm. in diameter; when they are more extensive, they coalesce and form larger, irregularly delimited, fairly thin, dry membranes. As long as the spots are not extensive, the intervening mucous membrane is more or less normal or only moderately hyperaemic. At an early stage, the spots are easily removed and the underlying mucous membrane is then found to be intact or only superficially eroded and moderately hyperaemic.

The Treatment of Moniliasis.

This consists of careful oral hygiene; washing and gargling with saturated sodium bicarbonate solution seems to be useful; in addition, intramuscular injections of vitamin B were employed and apparently with benefit; in cases where the larynx was involved, mercurochrome was applied. In pulmonary moniliasis treatment must be directed towards the maintenance of the patients,

state of nutrition; parenteral vitamin B complex seems to be of value.

In the mild cases, discontinuation of treatment with Corticotropin/Cortisone was not necessary. In more severe cases, discontinuation of such treatment may prove necessary; when this is the case, the withdrawal must take place very slowly, particularly if Cortisone has been administered over a prolonged period. As a maximum, the dose ought to be reduced by 12.5 mg. Cortisone every third day. The employment of Cortisone tablets of 5 mg, however, is preferable, the reduction being carried out by 5 mg every second, third or fourth day.

CONCLUSION

Until recently, moniliasis was encountered in adults only under very special circumstances and, by and large, the affection was only considered in infants.

The validity of this standpoint is obsolete as is seems apparent from the present account of a group of patients in whom the affection was encountered in 8—10 per cent out of well over 200 patients. Certainly, the majority of the cases of moniliasis were mild (11 out of 18) but severe cases occurred which were very troublesome and which constituted an extremely serious complication of the primary disease. This fact is a fresh reminder that treatment both with antibiotics and with Corticotropin/Cortisone should only be employed in cases where it is unquestionably indicated. Several other factors are contraindications against careless therapeutic or prophylactic sprinkling of the population with these exceedingly potent preparations which should not be brought into disrepute by being employed indiscriminately. The occurrence of moniliasis constitutes one such factor which must act as a break upon the not too uncommon happy-go-lucky therapeutic attitude.

SUMMARY

An account is given of 10 cases of moniliasis complicating treatment with antibiotics partly alone and partly in connection with Corticotropin/Cortisone, and of 8 cases of moniliasis in patients who had received Corticotropin/Cortisone but *no* treatment with antibiotics simultaneously or immediately preceeding. Cases like the last mentioned have to our knowledge not been recorded previously.

A more detailed account is given of 3 cases of severe moniliasis involving the oral cavity, the pharynx, the larynx and, in 2 of the cases, the lungs.

In 2 cases, generalized exanthema, developing suddenly, was observed; it is interpreted as moniliid, due to an allergic reaction caused by metabolic products of the Candida albicans.

References:

Ainsworth, G. C.: Medical Mycology, Pitman, London, 1952.

Andrews, G. C.: Diseases of the Skin, Saunders, Philadelphia, 1949, pag. 295 ff.

Brown, C., S. Propp, C. M. Guest, R. T. Beebe, L. Early: J. Am. Med. Ass. 1953, *152:* 206.

Finland, M. & L. Weinstein: New Engl. J. Med. 1953, *248:* 220.

Klingman, A. M.: J. Am. Med. Ass. 1950, *142:* 979.

Oblath, R. W., D. H. Donath, H. G. Johnstone & W. J. Kerr: Ann. Int. Med. 1951, *35:* 97.

Ormerod, F. C. & I. Friedman: Brit. Med. J. 1951, *2:* 1439.

Reimann, H. A.: Arch. Int. Med. 1953, *91:* 353.

Smith, D. T.: Ann. Int. Med. 1952, *37:* 1135.

Woods, J. W.: J. Am. Med. Ass. 1951, *145:* 207.

Wolff, F. W.: Lancet 1952, *1:* 1236.

Zettergren, L. & B. Sjöström: Acta Med. Scand. 1953, *147:* 203.

ADAMANTINOMAS AND MUCUS-SECRETING TUMOURS OF THE JAWS

By JOHN HERTZ

FREQUENCY AND OCCURRENCE

Adamantinomas and mucus-secreting tumours of the jaws are rare tumours. At Radiumhemmet in Stockholm, altogether 163,655 patients are on record in the thirty-year period of 1921—1950. Of these patients 1509 were suffering from tumours of the jaws; 31 (2 percent) of these tumours are registered as adamantinomas, whereas only 4 cases (2.7 *per mill)* concerned mucus-secreting tumours. The present paper is based upon all the cases of adamatinoma, 32 in all, treated at Radiumhemmet during the said period (3, 4, 5), and upon four cases of mucus-secreting tumours (6).

Adamantinomas most frequently involve the lower jaw, in the molar region. 6.6 percent of the tumours of the lower jaw are adamantinomas, whereas this kind of growth represents only 4.4 *per mill* of the tumours of the maxilla. In one of the author's cases (5), an adamantino-

From the Department of Radio-pathology, Karolinska Sjukhuset, Stockholm, Sweden.
(Former chief: *Olle Reuterwall;* present chief: *Lars Santesson).*

Published with a grant from »Kong Christian X's Fond«.

ma appeared in the tibia, an extremely rare location. In the entire medical literature there are only 24 cases on record of adamantinoma of the long bones.

Table 1.
Distribution according to the site of the adamantinomas:

	Adamantinomas	Jaw tumours in general
Upper jaw	16 % (5)	74.7 % (1,127)
Lower jaw	84 % (26)	25.3 % (382)
	31	1,509

In three of the author's cases, the mucus-secreting tumour was located in the lower jaw, whereas the upper jaw was involved in only one instance.

CLINICAL DATA

The adamantinomas are almost equally distributed according to sex, 18 patients (56 percent) being males and 14 (44 percent) females. All the patients with mucus-secreting tumours of the jaw — the author's cases as well as those on record in the literature — are females. Most of the patients noted their first symptoms at the age of 40—50 years.

Adamantinomas as well as mucus-secreting tumours appear as slow-growing swellings of the bone; it is the disfigurement rather than pain which brings these patients to the physician. Neuralgic pain or toothache may be present. In some cases the condition started as an epulis. The lump may be smooth or lobulated, and in a large number of cases it cracks like a lubricating can, especially if it is cystic. Soreness may develop; ulcers as well as fistulous tracts are not very uncommon, and secondary infection may result. The affected bone may break. Roentgen examination reveals a polycystic destruction of the bone with a honeycomb or soap-bubble appearance.

HISTO-PATHOLOGY

The adamantinomas are built up of a reticular stroma of connective tissue supporting irregularly anastomosing strands, islands and cords of epithelium. In the epithelium of the typical adamantinoma it is possible to distinguish between two kinds of cells, cylindric and stellate.

1. The epithelial areas are lined by a layer of cylindric cells forming palisades suggestive of ameloblas'ema. The nuclei are well defined, ovoid, rich in chromatin and located in the part of the cell most distant from the stroma. Fully developed teeth were observed in two of the cases.

2. The cells in the central parts of the epithelial areas are star-shaped, forming a stellate reticulum which resembles that seen in the enamel pulp.

The differentiation of the cells is highly varied, and very frequently a marked squamous-cell differentiation is in evidence. In some cases the cells in solid columns show a tendency to a concentric and whorl-like arrangement, with an increasing degree of keratinization towards the centres of the areas and the formation of "pearls", suggestive of a squamous-cell carcinoma with prickle cells. Further, smaller densely packed cuboidal cells may be seen, presenting the histologic pattern of a basal-cell carcinoma. In the central parts of the epithelial areas vacuolization takes place, the whole growth hereby assuming a cystic character.

The stroma varies considerably: in some cases it is scant, dense, hyaline; in others, abundant, rich in cells, sometimes to such a degree as to make the whole tumour resemble a sarcoma.

Consequently, based upon the histologic features as demonstrated by the cases under review, adamantinomas can be classified into the following six groups. (Table 2).

Table 2.
Classification of adamantinomas

1. Fully differentiated	9	18
» » with squamous-cell differentiation	9	
2. Rich in cells, but differentiated		3
3. Less differentiated but more highly so than a carcinoma		4
4. Suggestive af a squamous-cell carcinoma with prickle cells		2
5. Suggestive of a basal-cell carcinoma (including the tibial case)		4
6. Connective tissue predominant, suggestive of a fibrosarcoma		1
		32

The mucus-secreting tumours likewise consist of a reticular stroma of connective tissue supporting irregularly outlined solid and cystic islands, strands and cords of epithelial cells, the histologic over-all pattern being similar to that of adamantinoma. The secretion of mucus is a constant and typical feature.

The most important criterion in evaluating malignancy is, however, the behaviour of the tumour to the adjacent structures, especially the bone.

The findings in the histologic specimens suggest that the bony tissues are invaded and destroyed in the following manner: first the bony channels are invaded and filled with epithelial tumour vegetations. The destruction of the bone is then, obviously, caused by dissolution of the calcium, as a consequence of which the bone is transformed, first into osteoid masses and next into fascicles of collagen in between which the tumour cells penetrate. Further, in some places excavations resembling empty bone lacunae are observed. The collagen is further dissolved by the action of the tumour cells, and unmasked protoplasmic areas as well as areas of of "granular crumbling" (1, 2) occur in some places. Finally, remnants of collagen appear as a few fibrils forming a reti-

Table 3. *Outcome of treatment.* (Mucus-secreting tumours in brackets).

	Five year cure	Followed up less than five years - so far cured	Relapse	Relapse - died from tumour	Died from surgery	
Radical surgery	9	4	1			14
» » + irradiation	6		1 (2)	(1)	1	8 (3)
Conservative surgery	3	2	1			6
» » + irradiation	2		(1)			2 (1)
Irradiation			1	1		2
	20	6	4 (3)	1 (1)	1	32 (4)
	26		5 (4)			

culum in the meshes of which tumorous elements are in evidence.

The mucus-secreting epidermoid tumours seem to be less active in the destruction of the bone elements than the adamantinomas.

PATHOGENESIS

The numerous theories advanced concerning the genesis of the adamantinomas may be summarized in five main groups:

1. The morphology suggests that the tumour is derived from the epithelium of the foetal enamel organ or the tissue forming it.

2. Another theory ascribes their origin to supernumerary tooth germs.

3. A third attributes the origin of the adamantinomas to the "débris épithéliaux" of Malassez.

4. Less well known is the theory according to which adamantinomas are derived from simple dentigerous cysts.

5. The fifth theory claims that adamantinomas are derived from a post-foetal ingrowth of the epithelial lining of the gum.

It has been possible for the author to demonstrate very clearly in the histologic specimens how the proliferations extend from the lining stratified epithelium to form the epithelial areas which bear a striking resemblance to the enamel organ. In the author's opinion it is therefore most reasonable to consider the adamantinomas derived from the lining epithelium of the gum.

Embryologic features, the relationship of the jaws to the foregut, may be an explanation of the definite predominance of the adamantinomas in the lower jaw. The foregut in the oral floor extends to the area between the tongue and the anlage of the jaw, whereas in the upper part of the oral cavity it extends only slightly over the area which forms the isthmus of the fauces (Woerdeman). Because the substances which initiate the formation of the teeth probably are of a chemical nature, it seems most reasonable to assume that they have a more concentrated action upon the area of the lower jaw than upon that of the upper jaw.

The origin of the adamantinomas occurring in the long bones cannot be established on the basis of the author's case. Nor has it been possible to ascertain the origin of the mucus-secreting tumours of the jaws.

DIAGNOSIS

In establishing diagnosis, emphasis must be placed upon biopsy, which is our most important weapon. An aspiration biopsy is insufficient because an examination of the cyst membrane is imperative.

Even the histologic diagnosis may be fraught with the greatest difficulties. One of the author's cases of mucus-secreting tumours, for example, had been published previously as an adamantinoma "which has an unusual appearance microscopically"*) (8).

PROGNOSIS AND TREATMENT

The most important feature in evaluating the prognosis and establishing the proper treatment is the frequency of recurrence. Eight of the 32 patients with adamantinomas had had 2—4 recurrences before entry. 31 of the 32 patients have been followed up post-operatively; one patient had died from surgery. Of these 31 re-examined patients, 20 (65 percent) have been without relapse for more than five years. Of the 21 re-examined patients who were submitted to radical surgery, with or without irradiation, 15 (*71 percent*) have been without relapse for more than five years. (Table 3).

An entirely different picture is obtained if the tabulation is based upon the first therapeutic procedure to which the same patients have been submitted, at Radiumhemmet or elsewhere (Table 4). As mentioned, one patient died from surgery; this gives an *operative mortality rate of 3 percent.* Nine of the patients have been without relapse for more than 5 years (29 percent). 17 of the 18 patients who were treated with conservative surgery as the only therapeutic measure, have had relapses *(94 percent).* In the one case in which no recurrence has so far appeared, the observation period has, however, been only one year. The 21 recur-

*) This seems to justify Ahlbom's question "Have so-called atypical adamantinomas actually been mucous and salivary gland tumours?" (7).

Table 4. *Outcome of initial treatment.* (Mucus-secreting tumours in brackets).
Demonstrating the result of the first treatment to which *the same* patients have been submitted at Radiumhemmet or elsewhere.

	Five year cure	Followed up less than five years - so far cured	Relapse	Relapse - Died from tumour	Died from surgery	
Radical surgery	5		(1)			5 (1)
» » + irradiation	3		1 (1)		1	5 (1)
Conservative surgery		1	*16*	1		18
» » + irradiation .	1		1 (1)	(1)		2 (2)
Irradiation			2			2
	9	1	20 (3)	1 (1)	1	32 (4)
			21 (4)			

rent cases include the patient with tibial adamantinoma, which recurred 18 months after conservative surgery and was cured by a subsequent radical procedure; the observation period has now been more than 8 years.

One of the author's four patients with mucus-secreting tumours of the jaw died from her tumour, which recurred numerous times and extended to the base of the skull despite all therapeutic procedures attempted in the course of 16 years. One patient had a recurrence six years after surgery. The remaining two cases, with post-operative follow-up periods of 10 and 20 years, respectively, all show cures; in the latter case a metastatic node was removed 8 months after the primary surgery with the above mentioned favourable result.

It must further be emphasized that adamantinomas as well as mucus-secreting tumours of the jaws are relatively radioresistant, although the response of the mucus-secreting tumours to irridiation suggests a certain radiosensitivity. Adamantinomas and mucus-secreting tumours of the jaws must be considered "locally malignant". Several cases are, however, on record in which malignancy was not only "local" but where manifest metastases to the lungs and to the lymph nodes were observed, as in one of the author's cases.

The treatment of these types of tumour constitutes a serious surgical responsibility. It is of paramount importance that radical surgery be the primary line of attack; the fact remains that the *outcome of conservative procedures is nearly 100 percent recurrences* and that the *result of radical surgery is approximately 70 percent five-year cures.* Even the most heroic procedures will fail to keep away disaster if the primary treatment has been insufficient. In that case the surgeon, faced with impossible odds, can only say with J. R. Lowell:

There is no good in arguing with the inevitable.

References:

1) *Hertz, J.:* Studies on the healing of fractures with special reference to the significance of the vitamin content of the diet. Acta Path. Scand. 1936. Suppl. *28.*
2) *Hertz, J.:* Acta Path. Scand. 1936, *13:* 329.
3) *Hertz, J.:* Acta Med. Scand. 1952. Suppl. *266* (Papers dedicated to Erik Warburg), p. 529.
4) *Hertz, J.:* Acta Chir. Scand. 1951, *102:* 405.
5) *Hertz, J.:* Acta Orthopaed. 1952, *22:* 64.
6) *Hertz, J.:* Acta Chir. Scand. 1952, *103:* 276.
7) *Ahlbom, H. E.:* Mucous and salivary gland tumours. Acta Radiol. 1935. Suppl. *23.*
8) *McGregor, L.:* Acta Radiol. 1935, *16:* 254.

HYPERPARATHYROIDISM

INCIDENCE AND SURGICAL TREATMENT

By POUL FOGH-ANDERSEN

Primary hyperparathyroidism, virtually always due to adenoma formation in the parathyroid glands, was previously regarded as a rare condition, primarily significant as the cause of osteitis fibrosa. American reviews from recent years indicate, however, a relatively frequent incidence among patients with renal and ureteric calculi (4—8 per cent.). For more than 2 years, all patients in Department C, Rigshospitalet, suffering from urolithiasis were systematically examined for hyperparathyroidism; among 78 stone formers, 4 cases were encountered and operated upon, viz. an incidence of 5 per cent. Hyperparathyroidism is thus no rare condition and must be regarded as an important cause of stone formation in the

From the Department of Surgery C (Head: *E. Dahl-Iversen,* Professor of Surgery, University of Copenhagen), Rigshospitalet, Copenhagen.

urinary tract. Cases of bilateral renal calcinosis, in particular, should be suspected of hyperparathyroidism. It is important to establish the diagnosis early in patients suffering from urolithiasis and the condition should not only be considered in bilateral and relapsing cases. Further, the condition should be borne in mind in cases suffering from indefinite gastro-intestinal and nervous symptoms with vomiting and fatigue as the main complaints. Repeated determinations of serum Ca and P and quantitative determination of urinary Ca following a Ca-free diet will, as a rule, reveal hitherto undiscovered cases of hyperparathyroidism.

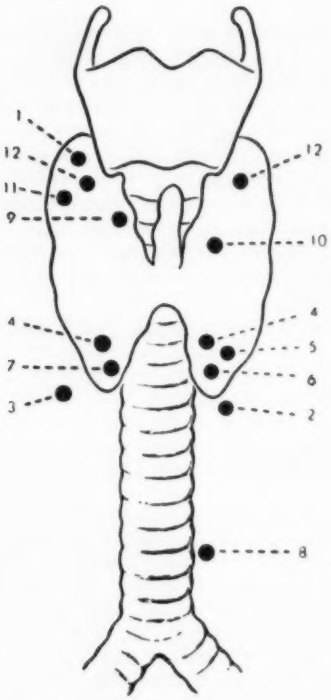


Figure 1.
Distribution of 14 parathyroid adenomata in relation to the trachea and (posterior aspect of) the thyroid gland in 12 patients operated upon.

In addition to the 4 cases mentioned above, and in the same period, 7 other patients were admitted from various medical departments and operated upon in Department C, Rigshospitalet, and one patient was operated upon 12 years ago (previously published by Espersen, 1944). From these 12 patients, a total of 14 adenomata of the parathyroid glands were removed at operation (Figure 1). In isolated patients, the operation gave rise to certain difficulties on account of ectopic situation of the adenomata (mediastinum). The size of the adenomata varied from that of a finger

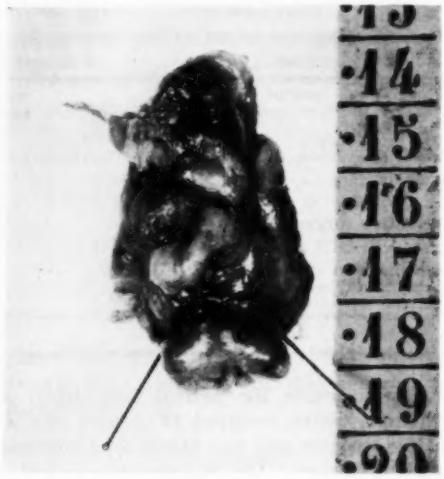


Figure 2.
Parathyroid adenoma weighing 12 gm., removed from a male, aged 29 years, with a cyst in the femur and bilateral renal calcinosis. Patient symptom-free 2 years after operation.

nail to large tumours of 12—17 gm. (Figure 2). None of the patients died in connection with the operation but one patient died from uraemia a month after discharge from the hospital. In one case, commencing malignant degeneration was revealed on histological examination.

A doubtless, although inexplicable connection between hyperparathyroidism and gastric and duodenal ulcer exists. Four of our 12 patients suffered from peptic ulceration and in one of them perforation occurred during hospitalization for the renal condition.

The long term prognosis is poor in untreated cases. On operative removal of the adenomata, the prognosis is dubious in advanced cases on account of impaired renal function. In the majority of his cases, Hellström found pronounced, progressive hypertension to which he ascribes conclusive prognostic significance. Among our 12 patients, only 4, however, suffered from hypertension and only 2 of these to a pronounced degree. Undoubtedly, a series of cases remains which may be permanently improved by operation, provided the diagnosis is established fairly early. Thus one of our 12 patients operated upon now feels completely fit and has normal Ca metabolism and blood pressure 12 years after extirpation of a large parathyroid adenoma which had given rise to marked symptoms.

Address: Solvej 2, Copenhagen.

References:
Fogh-Andersen, P.: Ugeskr. Læger 1954, *116:* 796.
Fogh-Andersen, P.: Acta Chir. Scand (in press).
Espersen, T.: Nord. Med. 1944, *22:* 894.
Hellström, J.: Acta Chir. Scand. 1953, *105:* 122.

THE LONG-TERM PROGNOSIS OF ACUTE NON-SPECIFIC PERICARDITIS

A FOLLOW-UP EXAMINATION INCLUDING CASES OF DRY PLEURISY FROM AN EPIDEMIC OF BORNHOLM DISEASE (MYALGIA EPIDEMICA) IN 1930—32.

By H. STORUP

The incidence of permanent sequelae following acute non-specific pericarditis is still obscure. The questions whether and how often constrictive pericarditis results, are of particular importance and if it does occur, how long the condition takes to develop. Levy & al. (12) did not find any sequelae in 23 patients from 6 months to 16 years after the acute pericarditis; Burchell (4) found no sequelae in 14 patients after the elapse of at least 5 years and none in 29 patients after 1—5 years. Carmichael & al. (5) did not find any case of constrictive pericarditis in 40 patients after the elapse of more than 2 years, but 2 patients had dyspnoea on exertion, 3 had slight oedema of the ankles in the evenings, one showed pericardial calcification at the apex while 6 showed electrocardiographic changes which could not be explained by other conditions. Bower & Gerrard (3) found 4 children to be healthy after an interval of 5½ years at the most and Tomlin (17) found no sequelae in one patient who had sustained 19 attacks of acute pericarditis in the course of 19 years. Hunter & East (9), on the other hand, encountered 2 cases of acute idiopathic pericarditis who developed constrictive pericarditis, verified at operation, in the course of approximately one year; Freilich (7) encountered one case with fixation of the heart, verified kymographically, following 3 acute attacks during a period of 5 years and Krook (10) found 2 cases of acute non-specific pericarditis which required operation for constrictive pericarditis after 6 and 20 months, respectively.

In certain accounts of constrictive pericarditis, acute non-specific pericarditis is stated as the cause of some of the cases. In Lassen's (11) post-mortem material of symphysis pericardii, the diagnosis of »pericarditis« was established in vivo in 3 patients. Paul, Castleman & White (14) found histories of acute pericarditis in 9 cases among 53 patients with constrictive pericarditis (17 per cent), and of those isolated idiopathic pericarditis in 7 cases. The latent period between acute pericarditis and constrictive pericarditis was short in 4 cases (soon after), in one case it was 10 years, in one case 29 years and in one case the period was not stated. Chambliss & al. (6) found histories of acute non-specific pericarditis in 3 cases out of 61 (4.9 per cent). In other accounts, acute non-specific pericarditis is not given as an etiological factor (2, 13).

From Medical Department B, Frederiksberg Hospital, Copenhagen.
Physician-in-Charge: *N. R. Christoffersen.*

MATERIAL

During the period 1930—44, 26 patients with the diagnosis of acute pericarditis were seen at Medical Department B, Frederiksberg Hospital. Twelve out of these patients died:

Two suffered from rheumatic fever, 4 from pneumonia, one from coronary thrombosis, one from cancer of the oesophagus, one from suppurative tuberculous mediastinal lymphadenitis and one from subacute

Table 1.
Acute, Non-Specific Pericarditis. Subjective and Objective Symptoms.

No.	Age	Sex	Catarrhal infection	Precordial pain	Pericardial friction rub	Radiologically demonstrable dilatation of the heart	E. C. G.
1. (1930)	18	♂	÷	+	+	÷ (7th day)	normal (8th day)
2. (1930)	32	♂	+	+	+	+	—
3. (1931)	19	♂	+	+	+	÷ (22nd day)	—
4. (1931)	25	♂	÷	+	+	÷ (20th day)	T_{2-3} ÷
5. (1932)	35	♂	+	+	÷ (10th day)	+	T_2 iso, T_3 ÷
6. (1932)	42	♀	÷	+	+	+	T_{1-2} ÷
7. (1933)	20	♂	+	+	+	÷	ST_1 raised
8. (1936)	25	♀	+	+	+	÷ (11th day)	normal (15th day)
9. (1938)	29	♀	÷	+	+	+	T_1 ÷, T_2 iso*)
10. (1942)	31	♀	÷	+	÷ (14th day)	+	T_1 iso, T_2 ÷*)

*) Typical electrocardiographical course, finally normal.

bacterial endocarditis as the primary condition; in 2 patients the etiology was obscure: one had haemopericardium, haemorrhagic pericarditis and coronary thrombosis (?) and one fibrinous pericarditis of unknown etiology.

Among the 14 surviving patients, 2 suffered from pulmonary tuberculosis and 2 from rheumatic fever while the remaining 10 must be classified in a group of *acute non-specific pericarditis*. Six of these 10 patients were from the years 1930—32. The subjective symptoms of these patients and the most important objective symptoms and findings appear in *Table 1*. It will be observed that all were young (only one was over 35 years of age) and that many had preceding catarrhal infection. All had precordial pain; in a number of cases, information concerning accentuation of the pain on coughing, swallowing or change of position was available. In all cases, at least one of the following symptoms or signs was observed: definite precordial friction rub, radiologically demonstrable increase of the heart shadow or electrocardiographic changes.

FOLLOW-UP EXAMINATION

Nine out of the 10 patients were alive at the time of the follow-up examination which in 6 cases occurred 20 to 22 years after the acute condition; in one case, the interval was 17 years and in 2 cases 11 and 10 years respectively. Eight patients were examined while one replied to a written questionnaire.

Recurrences:

One patient had probably 2 recurrences in the first year after discharge from hospital but was not examined by a physician nor admitted to a hospital; one had slight stabbing sensations in the precordium during catarrhal infections for the first years following admission to the hospital. None of the remaining patients had ever suffered from symptoms suggesting recurrence.

Subjective cardio-pulmonary complaints.

Three patients had suffered from slight dyspnoea on exertion ever since the acute pericarditis, but this had not increased with the years; one patient, as mentioned above, had slight stabbing pain in the chest during catarrhal infections for the first years but later became entirely symptom-free and one patient developed chronic bronchitis with slight dyspnoea on exertion after being symptom-free for 15 years (no. 6); 4 patients had been entirely free from symptoms; among these was the patient examined by the questionnaire.

Objective findings.

All 8 patients examined objectively showed normal findings on stethoscopic examination of the heart and the lungs; none showed enlargement of the liver, ascites nor oedema. X-ray examination showed the heart to be normal in size and no calcification was revealed (in 6 cases with at least 2 projections and in 2 cases with antero-posterior projection only).

In one case, a linear shadow was found in a small area of the left border of the heart which was not re-encountered in the lateral photographs (the patient was symptom-free). In one case (no. 6), the anterior heart contour in the lateral photograph was strikingly sharp bu not definitely pathological; unfortunately, kymography was not performed immediately and the patient could not be persuaded to come for renewed examination. In one case (no. 10), a well defined border was found along the right mediastinal margin, probabl a sequel of a mediastinal pleurisy; the kymographic oscillations corresponding to this border were negligible, but otherwise normal, particularly on the left side. The patient had slight dyspnoea on exertion. In the remaining 5 cases, the pictures were completely normal and among these was one patient (no. 7) with slight dyspnoea on exertion in whom kymography also revealed normal conditions. The pictures of the lungs were normal in all 8 cases.

Electrocardiograms were recorded from the 4 patients with subjective symptoms. These were normal in 3 cases while in the fourth patient (no. 6), who for 5 years had suffered from chronic bronchitis with some dyspnoea on exertion, the T-waves were low (T_1 0.5 mm., T_2 1 mm.).

One patient (no. 4) died prior to follow-up examination; the patient had diabetes mellitus and died from pneumonia over one year after the acute pericarditis. It appears from the casehistory that the patient complained of slight palpitations on exertion but not of dyspnoea. Stethoscopic examination of the heart, X-ray of the heart and electrocardiogram showed normal conditions. Permission for autopsy was not obtained.

PATIENTS WITH DRY PLEURISY DURING AN EPIDEMIC OF BORNHOLM DISEASE (MYALGIA EPIDEMICA)

In the literature, cases are described of constrictive pericarditis occurring after »pleurisy«. The combination of pericarditis plus pleurisy was frequent in the original Danish descriptions of acute benign pericarditis in Bornholm Disease (Bing (1), Heckscher (8)). These two conditions together with the fact that in certain cases it may be difficult to differentiate between (particularly left-sided) pleurisy with and without associated pericarditis, induced me also to investigate the patients who were admitted with idiopathic dry pleurisy during the epidemic of Bornholm Disease in 1930—32, viz. cases where no primary etiology for the pleurisy was present.

A total of 15 patients were concerned (including 6 from 1931 and 9 from 1932). 13 were under the age of 30 years. There were 8 males and 7 females. 13 patients were admitted in autumn; of these, 11 in the period of July-September. In addition to the pleurisy, a »blowing systolic murmur« was present over the heart in 3 cases, weak

in 2 cases and pronounced in one. X-ray examination of the heart did not demonstrate any definite abnormality and electrocardiography was not carried out. In one case, a male aged 41 years, there was in addition to bilateral pleurisy, radiologically demonstrable increase in the size of the heart, tendernes bemind the sternum and a friction rub in the second left intercostal space. No electrocardiogram was recorded. These 4 patients possibly had acute pericarditis in addition to the pleurisy. This is particularly probable in the case of the patient last mentioned.

FOLLOW-UP EXAMINATION

Three patients had died and three patients could not be traced.

One patient died in 1946 from cancer of the stomach, one in 1948 from suicide and one in 1948 from »sudden death«, probably heart disease. None of them were examined post-mortem. The patient who died suddenly was the man aged 41 in 1932 with suspected acute pericarditis.

Nine patients, including 2 of those suspected of having acute pericarditis, were traced, all 20—21 years after the acute condition. Three of them resided outside the capital and answered a written questionnaire; they were all symptom-free. Of the 6 patients also examined objectively, 3 were symptom-free, one had slight dyspnoea on exertion, one chronic bronchitis and dyspnoea on exertion and one will be mentioned in more detail below. In 5 cases, the objective clinical examination did not reveal any abnormality; none had oedema, enlargement of the liver nor ascites. X-ray photographs of the heart were normal in all cases. In the lungs, small areas of calcification were found in 3 cases and emphysema in one.

The sixth patient had suffered from a total of 3 nocturnal »attacks« with dyspnoea and without other cardiac complaints; in particular there was no dyspnoea on exertion. Objectively, a blowing systolic murmur, maximal over the aorta was audible. X-ray examination of the heart in several projections did not reveal any abnormality. The E.C.G. showed right-sided axis deviation and low isoelectric T_3. The vital capacity was 85 per cent. and the blood pressure 160/100 mm. Hg. The patient was admitted and the attacks were interpreted as probably tetany due to hyperventilation.

SUMMARY AND CONCLUSIONS

Among the total of 11 cases of verified constrictive pericarditis, described in the literature as occurring after acute idiopathic pericarditis and in which the latent interval from the acute pericarditis until the development of the constrictive pericarditis was stated, 8 developed less than 2 years after the acute condition and only one later than 10 years after. Only relatively few patients were examined 10 years or more after the acute condition.

Among the 10 patients with acute idiopathic pericarditis in the present material, including 6 from 1930—32, no case of constrictive pericarditis could be demonstrated in 1952—53 (at least 10 years after the acute condition) among the 9 survivors. In 15 patients with dry pleurisy, including 4 with additional, possibly acute pericarditis during an epidemic of Bornholm Disease in 1930—32, no cases of constrictive pericarditis were found after the lapse of at least 20 years among 9 of 12 survivors which could be contacted. The cases which died did not offer any positive criteria suggestive of constrictive pericarditis either, but autopsy was not performed on any. A number of patients had slight, non-progressive, subjective cardio-pulmonary complaints but were completely fit for work.

The risk of sustaining constrictive pericarditis following acute non-specific pericarditis seems thus to be limited mainly to the years immediately after the acute disease; during this period it is probably wise to keep these patients under regular observation. For patients with affections of the serous membranes during an epidemic of Bornholm Disease, the long term prognosis was favourable.

References:

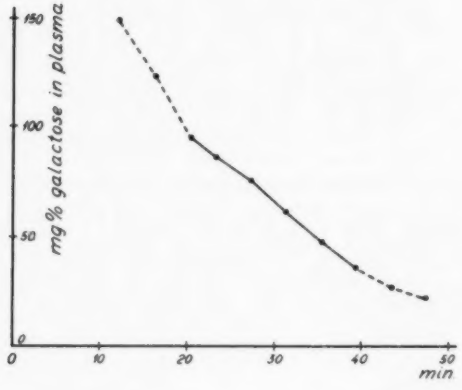
1) *Bing, H. J.:* Ugeskr. f. Læger 1933, *95:* 401.
2) *Blalock, A. & C. S. Burwell:* Surg. Gynec. & Obstr. 1941, *73:* 433.
3) *Bower, B. D. & J. Gerrard:* Brit. med. J. 1953, *1:* 244, 1953.
4) *Burchell, H. B.:* Mod. Concepts Cardiovas. Dis. 1947 (Marts) *16:* (n. p.)
5) *Carmichael, D. B., H. B. Sprague, S. M. Wyman & B. T. Bland:* Circulation 1951, *3:* 321.
6) *Chambliss, J. R., E. J. Januszewski, B. L. Brofman, J. F. Martin & H. Feil:* Circulation 1951, *4:* 816.
7) *Freilich, J. K.:* Ann. int. Med. 1952, *37:* 388.
8) *Heckscher, H.:* Ugeskr. f. Læger 1933, *95:* 402.
9) *Hunter, J. B. & T. East:* Lancet 1939, *1:* 255.
10) *Krook, H.:* Acta med. Scandinav. 1954, *148:* 201.
11) *Lassen, H. C. A.:* Ugeskr. f. Læger 1937, *99:* 567.
12) *Levy, R. L. & M. C. Patterson:* Am. J. Med. 1950, *8:* 34.
13) *Mortensen, V. & E. Warburg:* Acta med. Scandinav. 1948, *131:* 203.
14) *Paul, O., B. Castleman & P. D. White:* Am. J. Med. Sc. 1948, *216:* 361.
15) *Sylvest, E.:* Ugeskr. f. Læger 1930, *92:* 798.
16) *Sylvest, E.:* Den bornholmske syge. Myalgia epidemica. Thesis, Copenhagen 1933.
17) *Tomlin, C. R., R. B. Logue & J. W. Hurst:* J.A.M.A. 1952, *149:* 1215.

THE TIME COURSE OF THE BLOOD GALACTOSE CURVE AND ITS SIGNIFICANCE IN THE ESTIMATION OF LIVER FUNCTION

A PRELIMINARY COMMUNICATION

By NIELS TYGSTRUP and KJELD WINKLER

In attempts to determine the liver function by the amount of galactose removed from the blood per unit of time following a single injection of the substance, it appears that a part of the blood galactose graph may be demarcated which is straight. The Figure depicts such a curve.



It is maintained in the literature that the curve which expresses the time course of the galactose curve in the blood is exponential (Dominguez & Pomerene 1944, Stenstam 1946). As the question, whether an exponential or a straight graph is concerned is of decisive importance for the employability of the method in the investigation of the liver function, we made this question the subject of further investigation.

In doing this, we employed a method of analysis, published previously by us (Tygstrup, Winkler, Lund & Engell 1954), with a standard deviation of 1—2 mg %. Sixteen intravenous galactose loadings were undertaken on 12 healthy individuals and the curves obtained were treated statistically. The result of this is that within the mentioned fraction of the curve, galactose is removed in a constant quantity per unit of time, independently of the concentration. The removal may consequently be expressed according to the equation:

$$c = c_0 - gt$$

where c is the concentration, t is time and c_0 and g are constants.

From Medical Department B, Rigshospitalet, Copenhagen (Physician-in-Charge: Professor *E. Warburg*, M. D.).

It appears further from statistical analysis that the equation mentioned expresses the result with as great exactitude as the method of analysis permits.

References:

Dominguez, R. & E. Pomerene: Am. J. Physiol. 1944, *141:* 368.

Stenstam, T.: Acta med. Scandinav. 1946, Suppl. 177.

Tygstrup, N., K. Winkler, E. Lund & H. C. Engell: Scandinav. J. Clin. & Lab. Invest. 1954, *6:* 43.

Tygstrup, N. & K. Winkler: Acta Physiol. Scandinav. (in press).

LETTERS

To the Editor:

In view of numerous letters still reaching me, referring to statements in the lay press ascribing to me the discovery of a new dietary factor which cures gastric ulcer in man in 10—30 days, I would like to point out, that I have not announced such a discovery.

For a number of years I have, like several other investigators, studied the dietary development and prevention of gizzard ulcer in chicks. It is not known, at present, whether this subject is related to the human ulcer problem, but attempts to decide this question are in progress.

The above-mentioned newspaper articles mention a product said to cure gastric ulcer in man in a short time.

This product has been made on the initiative of the Danish-American manufacturer of pharmaceuticals Dr. Halfdan Hebo and called by him »Exul«. Dr. Hebo has fostered the idea of incorporating gizzard ulcer preventive factors in a milk diet and to have the product tested for its possible value in the treatment of gastric ulcer in man.

With a view of this, Dr. Hebo — whom I know from my stay in the U.S.A. — contacted me for collaboration and I would willingly have given him my support in development of the product and in the arrangement of the experiments required to judge its therapeutic value.

A qualification for such a collaboration was, of course, that the matter was conducted in a way compatible with scientific principles which would require that the product was not announced as curing human gastric ulcer at a time when clinical tests had not proved such a postulate. In view of the unfortunate development of the case I have had to terminate my cooperation in connection with this matter. Therefore, I wish to point out that I have not carried out animal tests with Dr. Hebo's product, and — not being a physician — I have not carried out clinical tests with it either.

Copenhagen, May 20, 1954. *Henrik Dam*